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The Journal of Allergy

VOL. 11 SEPTEMBER, 1940 No. 6

Original Articles

ANTIGENIC RELATIONSHIP OF COTTON LINTERS, DUST, AND DUST PRECURSORS

E. J. COULSON AND HENRY STEVENS
WASHINGTON, D. C.

AN INVESTIGATION directed primarily toward chemical characterization of the cottonseed allergens has included examination of the antigenic properties of cotton linters and other products segregated in milling the seed. This report deals in part with the study of three samples of cotton linters representing the short, low-grade fibers encountered principally in the chemical industries and two grades widely used in the manufacture of mattresses, felts, and upholstery. Cotton linters have acquired significance among allergists owing to the controversy concerning the origin and nature of house dust antigens. Therefore, methods found satisfactory for sensitization to linters were employed also for comparative studies of house dusts. Wool, egg white, and ragweed pollen were considered as possible precursors of the house dust antigens.

MATERIALS

It is probably impossible to attain the selection of a sample of cotton linters which would be representative of linters in general. Likelihood of contamination with extraneous materials will be recognized in the definition[1] of two factors, "foreign matter" and "color," which influence the grade or value and, consequently, the utility of cotton linters. "Foreign matter in linters consists of broken leaves, motes, sticks, dirt, and particles of the seed coat or hull that have been rasped off by the delinting saws, and the quantity present is influenced by the care exercised in cleaning the seed. The nature of the foreign matter varies in the different geographic sections of production." Colors other than those inherent to the fiber are sometimes found in linters. "They are usually the result of weather damage or fungous staining of the fiber, either while it is still on the undelinted seed or after it has been delinted and baled, through exposure of the bale."

In selection of linters for this study, attention was given to the grading of each sample because this factor serves to indicate the usual uses

From Allergen Investigations, Bureau of Agricultural Chemistry and Engineering, United States Department of Agriculture.

of the material and also provides a basis for controlling some of the numerous variables that might influence results.

Cotton Linters: A. I. No. 1. U. S. Grade No. 6.—This was obtained directly from the delinting machine in October, 1936, and stored in sealed glass until extracted. This is next to the lowest of the United States grades and is usually obtained by a second delinting to remove the short fibers growing close to the hull. These fibers are darker in color than the longer fibers obtained in the first cut and carry visible particles of the hull removed by the delinting saws. Linters of this grade are of too short staple for mattresses or upholstery, but are consumed in large quantities by industries as a source of cellulose.

A. I. No. 7. U. S. Grade No. 2.—This was obtained directly from the delinting machine in November, 1936, and stored in sealed glass until extracted. These relatively long-staple linters of creamy white color are widely used in mattresses and for other uses requiring well cleaned, unstained fibers relatively free from the short pigmented seed hairs and hull particles found in the lower grades.

A. I. No. 35. U. S. Grade No. 3.—This was obtained for immediate use from the Department of Agriculture grading pool in July, 1939. This grade is of shorter staple than U. S. Grade No. 2 and is generally used in mattresses and upholstery.

Cottonseed: A. I. No. 2.—These are prime quality whole cottonseed kernels (seed embryo) freed from endosperm, hull, and other parts of the seed.

Wool.—A sample of Rambouillet scoured wool was furnished by the Bureau of Animal Industry, United States Department of Agriculture.

House Dusts.—The *Dust P* sample was furnished by Dr. H. S. Bernton, Washington, D. C. The *Dust E* sample was furnished by Dr. B. G. Efron, New Orleans, La. The *Dust C* sample was collected from a vacuum cleaner in the home of one of the authors (E. J. C.).

Egg white was separated from fresh eggs.

Short ragweed pollen was taken from stock.

PREPARATION OF EXTRACTS

Cotton Linters Extracts.—Dilute linters extracts were aqueous extracts prepared by a technique previously described.[2]

Concentrated linters extracts were prepared by evaporating the dilute linters extracts in vacuum over phosphorus pentoxide to obtain a five- to seven-fold concentration.

Wool Extracts.—Dilute wool and concentrated wool extracts were aqueous extracts of scoured wool corresponding in technique of preparation to the dilute and concentrated linters extracts.

Cottonseed Extract.—Cottonseed kernels were exhaustively extracted with petroleum ether, dried, ground, extracted with ethyl ether, and freed from solvent. Five grams of the dried residue was mixed with 95 ml. of distilled water, saturated with toluene, and agitated for twenty-

four hours. The water extract was filtered and passed through a Seitz sterilizing pad.

House Dust Extracts.—Water extracts of house dust were prepared by the technique previously described,[2] using 20 Gm. of dust in 80 ml. of water.

Egg White.—Egg white was separated from fresh eggs, diluted with four volumes of distilled water, and filtered. Sodium chloride to 0.9 per cent was then added.

Ragweed Pollen Extracts: S.R.W. (1:100).—One gram of short ragweed pollen was extracted in 99 ml. of distilled water saturated with toluene for twenty-four hours with continuous agitation. The extract was sterilized by Seitz filtration. For the shocking injections sodium chloride was added to 0.9 per cent.

S.R.W. (1:20).—Five grams of short ragweed pollen was extracted with 95 ml. of distilled water in the same manner. For sensitizing injections, 10 per cent alum was added to a final concentration of 1 per cent, and the solution was adjusted to pH 7.0 as described previously.[2]

DIALYSIS OF THE HOUSE DUST EXTRACTS

Each house dust extract, in 20 ml. portions, was dialyzed at 6° C. for eleven days in cellophane tubes (wall thickness, 0.00072 inch) in two successive 20 ml. volumes of distilled water saturated with toluene. Dialysates were combined, evaporated in vacuo to dryness, and taken up with 5 ml. of 0.9 per cent sodium chloride solution. Dialysis of the original extracts was continued in running tap water at 10° C. for ten days.

The brown color of the dust extracts diffused into the collected dialysates, leaving the dialyzed solutions nearly free from color.

ANALYSIS OF EXTRACTS

Total nitrogen content of the extracts was determined by the Kjeldahl micromethod. No protein nitrogen was detected in the dilute cotton linters extract or in the three house dust extracts when analyzed by the trichloracetic acid procedure of Kunitz and Northrop.[3] (Table I.)

TABLE I

NITROGEN CONTENT OF EXTRACTS

EXTRACT	ORIGINAL	DIALYSATE	RESIDUE
Dilute linters AI#1	0.18*		
Concentrated linters AI#1	1.02		
Dilute linters AI#7	0.17		
Concentrated linters AI#7	0.87		
Dilute linters AI#35	0.15		
Dilute wool	0.09		
Concentrated wool	0.64		
Cottonseed	0.80		
Dust P	0.46	1.08	0.015
Dust E	0.65	1.50	0.015
Dust C	0.35	0.75	0.014

*Total nitrogen given in milligrams per milliliter.

TABLE II

COMPARISON OF SENSITIZATION OF GUINEA PIGS WITH COTTONSEED AND WITH COTTON LINTERS

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
78	330	Linters AI#7	27	459	1.0 ml. dilute linters AI#7	Moderate anaphylaxis
84	363	Linters AI#7	54	604	2.0 ml. dilute linters AI#7	Severe anaphylaxis
432	320	Linters AI#1	30	556	2.0 ml. dilute linters AI#1	Moderate anaphylaxis
444	318	Linters AI#1	29	520	3.0 ml. dilute linters AI#1	Moderate anaphylaxis
446	293	Linters AI#1	32	573	3.0 ml. dilute linters AI#1	Moderate anaphylaxis
489	305	Linters AI#1	47	413	4.0 ml. dilute linters AI#1	Fatal anaphylaxis, 4 min.
912	251	Linters AI#7	44	399	1.0 ml. dilute linters AI#1	Severe anaphylaxis
914	305	Linters AI#7	44	503	1.0 ml. dilute linters AI#1	Severe anaphylaxis
110	372	Linters AI#7	27	514	0.25 ml. cottonseed	None
111	358	Linters AI#7	71	573	0.30 ml. cottonseed	None
		30 min. later			1.25 ml. dilute linters AI#7	Severe anaphylaxis; died in night
142	355	Linters AI#7	133	739	1.50 ml. cottonseed	None
		30 min. later			2.0 ml. dilute linters AI#7	Moderate anaphylaxis
913	315	Linters AI#7	44	535	1.0 ml. cottonseed	Doubtful
		16 min. later			1.0 ml. dilute linters AI#7	Slight anaphylaxis
439	286	Linters AI#1	32	518	1.0 ml. cottonseed	None
		1 hour later			2.0 ml. dilute linters AI#1	None
441	292	Linters AI#1	29	455	1.0 ml. cottonseed	None
		30 min. later			3.0 ml. dilute linters AI#1	Moderate anaphylaxis
445	280	Linters AI#1	40	471	3.0 ml. cottonseed	None
		35 min. later			2.0 ml. dilute linters AI#1	Fatal anaphylaxis, 3 min.
493	307	Linters AI#1	64	466	2.0 ml. cottonseed	None
		1 hr. later			2.0 ml. dilute linters AI#7	None
907	250	Linters AI#1	44	477	1.0 ml. cottonseed	None
		17 min. later			1.0 ml. dilute linters AI#7	Fatal anaphylaxis, 5 min.

TABLE II—CONT'D

43	326	Cottonseed	21	518	0.2 ml. cottonseed	Fatal anaphylaxis, 4 min.
44	320	Cottonseed	21	491	0.04 ml. cottonseed	Fatal anaphylaxis, 4 min.
456	284	Cottonseed	27	583	0.1 ml. cottonseed	Moderate anaphylaxis
451	288	Cottonseed	33	729	0.2 ml. cottonseed	Severe anaphylaxis
459	292	Cottonseed	20	579	0.25 ml. cottonseed	Fatal anaphylaxis, 3 min.
458	329	Cottonseed	27	700	0.30 ml. cottonseed	Fatal anaphylaxis, 4 min.
54	297	Cottonseed	21	427	1.0 ml. dilute linters AI#7	None
		10 min. later			0.05 ml. cottonseed	Slight anaphylaxis
45	272	Cottonseed	21	415	1.0 ml. dilute linters AI#7	None
		10 min. later			0.04 ml. cottonseed	Severe anaphylaxis
487	275	Cottonseed	47	418	4.5 ml. dilute linters AI#7	None
		25 min. later			0.05 ml. cottonseed	Fatal anaphylaxis, 4 min.
443	294	Cottonseed	32	393	3.0 ml. dilute linters AI#1	None
		1 hr. later			0.3 ml. cottonseed	Severe anaphylaxis
435	294	Cottonseed	30	496	5.0 ml. dilute linters AI#1	None
		40 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 4 min.
498	293	Cottonseed	64	665	5.0 ml. dilute linters AI#7	None
		80 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 3 min.
490	265	Cottonseed	64	573	4.6 ml. dilute linters AI#7	None
		1 hr. later			0.2 ml. cottonseed	Slight anaphylaxis
917	291	Cottonseed	16	380	1.0 ml. conc. liters AI#7	None
		40 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 4½ min.
918	267	Cottonseed	44	525	1.0 ml. dilute linters AI#7	None
		24 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 3½ min.
919	228	Cottonseed	47	430	1.0 ml. dilute linters AI#7	Doubtful
		28 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 4½ min.
924	258	Cottonseed	47	557	1.0 ml. dilute linters AI#1	Delayed; doubtful
		30 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 4 min.
925	227	Cottonseed	47	457	1.0 ml. dilute linters AI#1	None
		25 min. later			0.2 ml. cottonseed	Fatal anaphylaxis, 4½ min.

SENSITIZATION OF GUINEA PIGS

Guinea pigs were sensitized to cotton linters, house dusts, wool, and pollen by subcutaneous injection of 2.0 ml. of alum-precipitated extracts.[2] Sensitization to cottonseed was by a single intraperitoneal injection of 1.0 ml. of the aqueous cottonseed extract to which sodium chloride was added to a concentration of 0.9 per cent.

Shocking injections were made intravenously with the aqueous extracts to which 0.9 per cent sodium chloride was added.

Response to the shocking injection was classified by the system proposed by Wells and Osborne,[4] omitting consideration of body temperature changes.

EXPERIMENTAL

SENSITIZATION WITH COTTON LINTERS AND COTTONSEED

Objectives of the experiments recorded in Table II were: (a) to demonstrate sensitization to cotton linters of two grades, U. S. No. 6 and U. S. No. 2; (b) to determine whether antigens of the seed hairs and seed kernel could be distinguished; and (c) to determine whether antigens of the seed kernel were present in low-grade (second cut) linters or in high-grade (first cut) linters.

Results obtained in this series demonstrated successful sensitization of guinea pigs to a water-soluble antigen present in linters representative of two grades differing widely in commercial quality and utility. Antigens of the seed hairs and seed kernel were clearly distinguished. None of the antigen of the cottonseed kernel (embryo) was detected in samples of linters representing high and low grades. These findings supplement and confirm the results reported by Cohen, Cohen, and Hawver.[5]

SENSITIZATION TO HOUSE DUSTS

Results recorded in Table III demonstrated anaphylactic sensitization of guinea pigs with three house dust extracts. Evidence of marked differences in antigenic potency among the dust extracts noted in these results was confirmed in subsequent crossed reactions. No correlation was found between antigenic potency and nitrogen content of the different extracts.

Administration of relatively large doses of the extracts of Dusts E and P in nonsensitized control animals induced symptoms of shock differing from anaphylaxis. This reaction has been previously reported[2, 6] and attributed to a nonspecific toxic factor. Dust C, which yielded extracts of highest antigenic activity, appeared to be relatively free from the nonspecific factor.

CROSSED REACTIONS BETWEEN HOUSE DUSTS FROM THREE SOURCES

Crossed reactions with extracts from three samples of dust (Table IV) revealed differences in potency in producing symptoms of anaphylaxis among heterologously sensitized animals. Dust P extract, which

TABLE III

SENSITIZATION TO HOUSE DUSTS

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
667	244	Dust P	34	442	0.8 ml. Dust P	None
683	244	Dust P	34	369	0.8 ml. Dust P	Slight anaphylaxis
686	244	Dust P	34	512	0.8 ml. Dust P	Severe anaphylaxis
883	342	Dust P	36	462	0.8 ml. Dust P	None
661	246	Dust P	34	422	1.2 ml. Dust P	Moderate anaphylaxis
1042		None; Control		431	2.0 ml. Dust P	None
1043		None; Control		461	3.0 ml. Dust P	None
1044		None; Control		448	4.0 ml. Dust P	Delayed slight anaphylactoid
740		None; Control		351	4.0 ml. Dust P	Severe anaphylactoid
668	271	Dust E	34	523	0.4 ml. Dust E	Severe anaphylaxis
677	234	Dust E	34	450	0.4 ml. Dust E	Moderate anaphylaxis
681	223	Dust E	34	407	0.4 ml. Dust E	Fatal anaphylaxis, 4 min.
889	245	Dust E	36	460	0.5 ml. Dust E	Moderate anaphylaxis
741		None; Control		287	1.0 ml. Dust E	None
1025		None; Control		599	1.0 ml. Dust E	None
723		None; Control		378	2.0 ml. Dust E	None
1026		None; Control		545	2.0 ml. Dust E	Delayed slight anaphylactoid
935		None; Control		417	3.0 ml. Dust E	None
1027		None; Control		551	3.0 ml. Dust E	None
725		None; Control		496	4.0 ml. Dust E	None
1028		None; Control		550	4.0 ml. Dust E	Delayed slight anaphylactoid
663	234	Dust C	34	442	0.8 ml. Dust C	Fatal anaphylaxis, 15 min.
674	230	Dust C	34	398	0.8 ml. Dust C	Fatal anaphylaxis, 8 min.
881	279	Dust C	36	418	0.5 ml. Dust C	Fatal anaphylaxis, 4½ min.
926		None; Control		393	3.0 ml. Dust C	None
931		None; Control		407	3.0 ml. Dust C	None
736		None; Control		384	4.0 ml. Dust C	None
1045		None; Control		448	4.0 ml. Dust C	None

induced the weakest reactions in homologously sensitized animals, caused doubtful or no symptoms of anaphylaxis in animals sensitized with Dust E, and it produced from slight to fatal anaphylaxis in guinea pigs sensitized with Dust C. Extracts of Dust E or C induced from slight to severe anaphylaxis in animals sensitized to Dust P. These results indicated the presence of an antigen common to all three samples.

REACTION TO DIALYSIS PRODUCTS OF HOUSE DUST EXTRACTS

The results in Table V show that the dialysate from Dust P did not induce anaphylaxis in an animal sensitized to the original Dust P extract. Moreover, the Dust P dialysate did not desensitize to a subse-

quent injection of the dialyzed Dust P extract. Dialysates from Dusts E and C induced anaphylaxis in animals sensitized to the original E and C extracts, respectively. One animal, No. 655, sensitized to Dust P, exhibited moderate anaphylaxis when injected with the dialysate of Dust C. No appreciable decrease in anaphylactogenic potency of the dust extracts could be detected after prolonged dialysis. Evidence of the nonspecific toxic factor in Dust E appeared when relatively large doses of the dialysate or the dialyzed extracts were administered in control tests.

TABLE IV

CROSSED REACTIONS BETWEEN HOUSE DUSTS FROM THREE SOURCES

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
568	264	Dust P	33	489	0.4 ml. Dust E	Slight anaphylaxis
572	300	Dust P	33	536	0.4 ml. Dust E	Slight anaphylaxis
660	264	Dust P	52	560	0.5 ml. Dust E	Severe anaphylaxis
685	248	Dust P	34	421	0.8 ml. Dust C	Moderate anaphylaxis
885	314	Dust P	47	597	0.8 ml. Dust C	Fatal anaphylaxis, 3½ min.
567	263	Dust E	33	470	0.8 ml. Dust P	None
		50 min. later			0.4 ml. Dust E	Slight anaphylaxis
570	350	Dust E	33	670	1.0 ml. Dust P	Doubtful
		19 min. later			0.4 ml. Dust E	Moderate anaphylaxis
682	255	Dust E	34	426	0.8 ml. Dust C	Fatal anaphylaxis, 5 min.
656	262	Dust E	39	446	0.8 ml. Dust C	Moderate anaphylaxis
689	277	Dust C	38	477	0.8 ml. Dust P	Fatal anaphylaxis, 4 min.
974	203	Dust C	46	366	1.0 ml. Dust P	Slight anaphylaxis
		42 min. later			1.0 ml. Dust C	Fatal anaphylaxis, 4½ min.
976	283	Dust C	46	536	1.0 ml. Dust P	Slight anaphylaxis
		44 min. later			1.0 ml. Dust C	Fatal anaphylaxis, 11 min.
666	263	Dust C	38	522	0.5 ml. Dust E	Fatal anaphylaxis, 15 min.
675	253	Dust C	38	443	0.5 ml. Dust E	Fatal anaphylaxis, 32 min.

HOUSE DUSTS AND COTTON LINTERS

Crossed reactions with extracts of house dusts and cotton linters (Table VI) indicated that an antigen common to both can usually be demonstrated. The data presented are unselected and illustrate, therefore, the range of variable results which might reasonably be anticipated with substances differing significantly in origin and history. The common antigen in the dust extracts was present in quantities sufficiently great to sensitize to linters extract, but too small to induce severe shock in animals sensitized with linters extract. The range and order of antigenicity of the three dust extracts in sensitizing animals

TABLE V

REACTIONS TO DIALYSIS PRODUCTS OF HOUSE DUST EXTRACTS

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
650	264	Dust P	38	415	0.8 ml. Dust P residue	Severe anaphylaxis
691	270	Dust P	38	464	0.5 ml. Dust P dialysate	None
		50 min. later			0.8 ml. Dust P residue	Slight anaphylaxis
708	270	Dust P	52	510	1.0 ml. Dust P dialysate	None
		36 min. later			0.8 ml. Dust C residue	Severe anaphylaxis
655	253	Dust P	38	443	0.5 ml. Dust C dialysate	Moderate anaphylaxis
651	251	Dust E	34	487	0.5 ml. Dust E dialysate	Slight anaphylaxis
679	257	Dust E	34	533	0.5 ml. Dust E dialysate	Moderate anaphylaxis
690	263	Dust E	34	376	0.5 ml. Dust E dialysate	Slight anaphylaxis
684	237	Dust E	34	408	0.5 ml. Dust E residue	Moderate anaphylaxis
662	253	Dust C	35	425	0.5 ml. Dust C dialysate	Severe anaphylaxis
678	250	Dust C	35	485	0.5 ml. Dust C dialysate	Moderate anaphylaxis
687	257	Dust C	38	496	0.8 ml. Dust C residue	Fatal anaphylaxis, 8 min.
688	261	Dust C	38	427	0.8 ml. Dust C residue	Fatal anaphylaxis, 5 min.
737		None; Control		370	0.5 ml. Dust E dialysate	None
732		None; Control		375	1.0 ml. Dust E dialysate	Moderate anaphylactoid
720		None; Control		342	1.0 ml. Dust C dialysate	None
721		None; Control		366	1.0 ml. Dust C dialysate	None
738		None; Control		341	4.0 ml. Dust E residue	Delayed moderate anaphylactoid
742		None; Control		356	4.0 ml. Dust E residue	None

TABLE VI

COMPARISON OF SENSITIZATION OF GUINEA PIGS WITH HOUSE DUSTS AND WITH COTTON LINTERS

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
665	205	Linters AI#7	38	355	1.0 ml. concentrated linters AI#7	Fatal anaphylaxis, 17 min.
680	197	Linters AI#7	49	452	0.5 ml. concentrated linters AI#7	Fatal anaphylaxis, 3½ min.
706	305	Linters AI#7	39	521	1.0 ml. Dust P	None
		15 min. later			1.0 ml. concentrated linters AI#7	Slight anaphylaxis
1001	308	Linters AI#7	46	579	1.0 ml. Dust P	Slight anaphylaxis
		56 min. later			2.0 ml. dilute linters AI#7	Severe anaphylaxis
1006	283	Linters AI#7	46	497	1.0 ml. Dust P	Doubtful
		36 min. later			2.0 ml. dilute linters AI#7	Severe anaphylaxis
694	287	Linters AI#7	39	501	1.0 ml. Dust E	Doubtful
		30 min. later			1.0 ml. concentrated linters AI#7	Severe anaphylaxis
1014	296	Linters AI#7	45	591	1.0 ml. Dust E	Moderate anaphylaxis
1015	236	Linters AI#7	45	498	1.0 ml. Dust E	Slight anaphylaxis
692	316	Linters AI#7	39	532	1.0 ml. Dust C	None
		30 min. later			1.0 ml. concentrated linters AI#7	Slight anaphylaxis
1008	298	Linters AI#7	49	548	1.0 ml. Dust C	Doubtful
		47 min. later			2.0 ml. dilute linters AI#7	Severe anaphylaxis
1013	304	Linters AI#7	49	565	1.0 ml. Dust C	Slight anaphylaxis
		47 min. later			2.0 ml. dilute linters AI#7	Fatal anaphylaxis, 5½ min.
904	253	Linters AI#1	47	486	1.0 ml. Dust P	None
		34 min. later			1.0 ml. dilute linters AI#1	Slight anaphylaxis
1019	286	Linters AI#1	45	558	1.0 ml. Dust E	Severe anaphylaxis

TABLE VI—CONT'D

657	240	Dust P	45	421	1.0 ml. concentrated linters AI#7	Moderate anaphylaxis
884	340	Dust P	38	550	1.0 ml. concentrated linters AI#7	Moderate anaphylaxis
969	319	Dust P	49	530	2.0 ml. dilute linters AI#7	Slight anaphylaxis
967	270	Dust P	52	451	2.0 ml. dilute linters AI#35	None
702	259	Dust E	41	402	1.0 ml. concentrated linters AI#7	Severe anaphylaxis
893	294	Dust E	38	515	1.0 ml. concentrated linters AI#7	Severe anaphylaxis
981	259	Dust E	49	458	2.0 ml. dilute linters AI#7	Slight anaphylaxis
984	348	Dust E	52	576	2.0 ml. dilute linters AI#35	None
987	249	Dust E	52	461	2.0 ml. dilute linters AI#35	None
669	288	Dust C	41	524	1.0 ml. concentrated linters AI#7	Fatal anaphylaxis, 5 min.
705	288	Dust C	45	431	1.0 ml. concentrated linters AI#7	Fatal anaphylaxis, 13 min.
977	300	Dust C	49	535	2.0 ml. dilute linters AI#7	Fatal anaphylaxis, 4 min.
1018	269	Linters AI#7	49	461	2.0 ml. dilute linters AI#35	None
		25 min. later			2.0 ml. dilute linters AI#7	Fatal anaphylaxis, 5 min.
1020	291	Linters AI#1	51	611	2.0 ml. dilute linters AI#35	Slight anaphylaxis
		27 min. later			2.0 ml. dilute linters AI#7	Prostration
1021	307	Linters AI#1	52	629	2.0 ml. dilute linters AI#35	Moderate anaphylaxis
748		None; Control		330	1.0 ml. concentrated linters AI#7	None
751		None; Control		300	1.0 ml. concentrated linters AI#7	None
774		None; Control		352	3.0 ml. concentrated linters AI#7	Slight anaphylactoid; died during night
1047		None; Control		456	2.0 ml. concentrated linters AI#7	Delayed; doubtful
1048		None; Control		449	2.0 ml. concentrated linters AI#7	Delayed; doubtful
930		None; Control		357	2.5 ml. concentrated linters AI#7	None
1032		None; Control		558	0.5 ml. concentrated linters AI#35	None
1056		None; Control		452	2.0 ml. concentrated linters AI#7	None
1039		None; Control		433	4.0 ml. concentrated linters AI#7	Delayed doubtful anaphylactoid

to cotton linters were the same as previously noted in the comparison of their potencies on the basis of crossed reactions of dust versus dust.

MULTIPLE SENSITIVITY OF HOUSE DUST SENSITIZED ANIMALS

In Table VII are shown results obtained when four guinea pigs, sensitized to house dusts, were desensitized to cotton linters by a series of intraperitoneal injections of the dilute linters extract. Three of these guinea pigs thus desensitized exhibited no reaction when 0.5 ml. of the concentrated linters extract was subsequently injected intravenously. The fourth animal, which had shown the most marked symptoms during the desensitizing doses, reacted with slight anaphylaxis upon the injection of the concentrated linters extract. All four of the above-described animals, when subsequently injected with house dust extracts, exhibited symptoms of anaphylaxis which in two cases resulted fatally.

Animal No. 676 is of considerable interest. This animal, originally sensitized to Dust E, was desensitized to the cotton linters component and still exhibited fatal anaphylaxis upon injection of Dust C. This indicated that there was more than one common antigen in these two dusts, the cotton linters principle being one of them.

HOUSE DUST AND WOOL

Wool fibers can usually be identified in dusts from houses furnished with rugs and carpets. This fact suggested an attempt to detect a common antigen in extracts of wool, house dusts, and cotton linters (Table VIII). Among ten animals sensitized with house dust extracts and tested with concentrated wool extract, five exhibited no symptoms of anaphylaxis and five responded with symptoms ranging from a doubtful reaction to fatal shock. Three of the five negative reactions were among animals sensitized with extract of Dust E in which no wool antigen could be detected. Three of five animals sensitized to wool exhibited no symptoms when tested with house dust extracts. Reactions of the other two animals of this group, classified as doubtful and slight anaphylaxis, were of questionable significance, but possibly were indicative of wool antigen in extracts of Dusts P and C. Wool extract induced no symptoms of anaphylaxis when injected into animals sensitized with cotton linters extract and did not diminish the sensitivity to linters extract. Data recorded in this series are unselected and include, therefore, three final tests which showed no evidence of sensitization to either wool or linters. No indications of inherent toxicity of the concentrated wool extract were observed.

HOUSE DUST AND EGG WHITE

Results recorded in Table IX provided evidence confirming the presence of egg white antigen in Dusts P, E, and C. Indications of the

TABLE VII

MULTIPLE SENSITIVITY OF HOUSE DUST SENSITIZED ANIMALS

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION		SYMPTOMS
693	288	Dust C	46	601	3.0 ml. dilute linters	i.p.*	Slight anaphylaxis
		24 hr. later, not fully recovered		560	3.0 ml. dilute linters	i.p.	Slight anaphylaxis
		24 hr. later, improved		537	5.0 ml. dilute linters	i.p.	Slight anaphylaxis
		4½ hr. later			0.5 ml. concentrated linters	i.v.†	Slight anaphylaxis
		1 hr. later, recovered from convulsive attack, but moribund			0.8 ml. Dust C	i.v.	Fatal anaphylaxis, 4 min.
700	288	Dust C	46	551	3.0 ml. dilute linters	i.p.	Slight anaphylaxis
		24 hr. later, entirely recovered		537	3.0 ml. dilute linters	i.p.	Slight anaphylaxis
		24 hr. later, entirely recovered		549	5.0 ml. dilute linters	i.p.	Slight anaphylaxis
		4½ hr. later			0.5 ml. concentrated linters	i.v.	None
		37 min. later			0.5 ml. Dust P	i.v.	Doubtful anaphylaxis
		25 min. later			0.8 ml. Dust C	i.v.	Slight anaphylaxis
676	250	Dust E	46	621	3.0 ml. dilute linters	i.p.	Doubtful; slight discomfort
		24 hr. later, no symptoms		603	4.0 ml. dilute linters	i.p.	Slight uneasiness
		24 hr. later, no symptoms		590	5.0 ml. dilute linters	i.p.	Uneasiness; quickly passed off
		3 hr. later			0.5 ml. concentrated linters	i.v.	None
		40 min. later			0.8 ml. Dust C		Fatal anaphylaxis, 51 min.
710	288	Dust E	46	523	3.0 ml. dilute linters	i.p.	Slight discomfort
		24 hr. later, no symptoms		500	4.0 ml. dilute linters	i.p.	Slight discomfort
		24 hr. later, no symptoms		504	5.0 ml. dilute linters	i.p.	Slight uneasiness; quickly passed off
		4 hr. later			0.5 ml. concentrated linters	i.v.	None
		37 min. later			0.5 ml. Dust E	i.v.	Severe anaphylaxis
711		None; Control		577	3.0 ml. dilute linters	i.p.	None
		24 hr. later, no symptoms		563	5.0 ml. dilute linters	i.p.	Slight uneasiness; quickly passed off
		24 hr. later, no symptoms		551	5.0 ml. dilute linters	i.p.	Slight uneasiness; quickly passed off
		3½ hr. later, no symptoms			1.0 ml. Dust E	i.v.	None

*i.p., intraperitoneal.
†i.v., intravenous.

TABLE VIII

COMPARISON OF SENSITIZATION OF GUINEA PIGS WITH HOUSE DUSTS AND WITH WOOL.

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
886	291	Dust P	66	675	1.0 ml. concentrated wool	None
		45 min. later			1.0 ml. Dust P	Moderate anaphylaxis
887	301	Dust P	37	530	1.0 ml. concentrated wool	Fatal anaphylaxis, 3½ min.
972	343	Dust P	49	482	1.0 ml. concentrated wool	Slight anaphylaxis
891	298	Dust E	36	411	1.0 ml. concentrated wool	None
892	311	Dust E	37	497	1.0 ml. concentrated wool	None
		1 hr. later			0.5 ml. Dust E	Moderate anaphylaxis
982	299	Dust E	51	483	2.0 ml. concentrated wool	None
		1 hr. later			0.8 ml. Dust E	Fatal anaphylaxis, 5 min.
878	241	Dust C	36	406	0.8 ml. concentrated wool	None
		1 hr. later			0.8 ml. Dust C	Fatal anaphylaxis, 5½ min.
879	280	Dust C	37	490	1.0 ml. concentrated wool	Moderate anaphylaxis
880	273	Dust C	37	424	1.0 ml. concentrated wool	Moderate anaphylaxis
978	305	Dust C	49	561	1.0 ml. concentrated wool	Doubtful
		31 min. later			1.0 ml. Dust C	Fatal anaphylaxis, 5 min.
894	272	Wool	36	498	0.5 ml. concentrated wool	Fatal anaphylaxis, 7 min.
896	261	Wool	37	493	1.0 ml. Dust P	None
		1½ hr. later			0.5 ml. concentrated wool	Moderate anaphylaxis

TABLE VIII—CONT'D

993	339	Wool	46	506	1.0 ml. Dust P	None
		17 min. later			1.0 ml. concentrated wool	Slight anaphylaxis
989	349	Wool	45	550	0.6 ml. Dust E	Doubtful
		34 min. later			1.0 ml. concentrated wool	Slight anaphylaxis
895	308	Wool	37	525	1.0 ml. Dust C	Slight anaphylaxis
		2 hr. later			0.5 ml. concentrated wool	Moderate anaphylaxis
988	229	Wool	49	416	1.0 ml. Dust C	None
		41 min. later			1.0 ml. concentrated wool	None
1038		None; control		557	2.0 ml. concentrated wool	None
908	261	Linters AI#7	44	425	1.0 ml. concentrated wool	None
		30 min. later			1.0 ml. dilute linters AI#7	Fatal anaphylaxis, 4½ min.
909	249	Linters AI#7	44	427	1.0 ml. concentrated wool	None
		23 min. later			1.0 ml. dilute linters AI#7	Fatal anaphylaxis, 5 min.
1016	245	Linters AI#7	51	478	2.0 ml. concentrated wool	None
		44 min. later			2.0 ml. dilute linters AI#7	Severe anaphylaxis
1017	236	Linters AI#7	51	430	2.0 ml. concentrated wool	None
		41 min. later			2.0 ml. dilute linters AI#7	Fatal anaphylaxis, 4½ min.
897	326	Wool	66	595	1.0 ml. dilute linters AI#7	None
		30 min. later			1.0 ml. concentrated wool	None
994	289	Wool	52	461	2.0 ml. dilute linters AI#7	None
		45 min. later			2.0 ml. concentrated wool	Doubtful
1000	320	Wool	52	549	2.0 ml. dilute linters AI#7	None
		37 min. later			2.0 ml. concentrated wool	None

TABLE IX

COMPARISON OF SENSITIZATION OF GUINEA PIGS WITH HOUSE DUSTS AND WITH EGG WHITE

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
970	333	Dust P	51	595	1.0 ml. egg white (1:5)	Fatal anaphylaxis, 3 min.
975	300	Dust P	51	579	0.3 ml. egg white (1:5)	None
1106	231	Dust P	36	433	0.2 ml. egg white (1:5)	None
		40 min. later			1.0 ml. Dust P	Severe anaphylaxis
1109	271	Dust P	36	457	0.5 ml. egg white (1:5)	Fatal anaphylaxis, 3½ min.
984	348	Dust E	52	576	0.5 ml. egg white (1:5)	Fatal anaphylaxis, 4½ min.
985	309	Dust E	51	506	0.5 ml. egg white (1:5)	Fatal anaphylaxis, 4½ min.
987	249	Dust E	52	461	0.2 ml. egg white (1:5)	Fatal anaphylaxis, 4½ min.
1102	252	Dust E	36	553	0.2 ml. egg white (1:5)	Fatal anaphylaxis, 4 min.
980	298	Dust C	51	491	0.5 ml. egg white (1:5)	Fatal anaphylaxis, 4½ min.
1098	260	Dust C	36	382	0.1 ml. egg white (1:5)	Fatal anaphylaxis, 5 min.
959	233	S.R.W.*	131	683	1.0 ml. egg white (1:5)	None
		25 min. later			0.3 ml. S.R.W. (1:100)	Fatal anaphylaxis, 5½ min.
1114	305	S.R.W.	21	427	1.0 ml. egg white (1:5)	None
		28 min. later			0.3 ml. S.R.W. (1:100)	Fatal anaphylaxis, 6 min.
1054		None; Control		436	1.0 ml. egg white (1:5)	None
1069		None; Control		469	1.0 ml. egg white (1:5)	None

*S.R.W., short ragweed pollen extract.

TABLE X

COMPARISON OF SENSITIZATION OF GUINEA PIGS WITH HOUSE DUSTS AND WITH RAGWEED POLLEN

ANIMAL NO.	BODY WEIGHT (GM.)	SENSITIZED TO	INCUBATION PERIOD (DAYS)	BODY WEIGHT (GM.)	TEST INJECTION	SYMPTOMS
968	292	Dust P	51	614	0.5 ml. (1:20) S.R.W.*	Doubtful
		30 min. later			1.0 ml. Dust P	None
983	339	Dust E	51	556	0.5 ml. (1:20) S.R.W.	None
		25 min. later			0.8 ml. Dust E	Fatal anaphylaxis, 4½ min.
979	233	Dust C	51	367	0.5 ml. (1:20) S.R.W.	None
		21 min. later			1.0 ml. Dust C	Fatal anaphylaxis, 4 min.
956	250	S.R.W.	81	685	1.0 ml. Dust P	None
		17 min. later			0.2 ml. (1:100) S.R.W.	Fatal anaphylaxis, 4 min.
957	287	S.R.W.	81	591	1.0 ml. Dust E	None
		14 min. later			0.2 ml. (1:100) S.R.W.	Fatal anaphylaxis, 3 min.
958	221	S.R.W.	81	559	2.0 ml. Dust C	None
		13 min. later			0.2 ml. (1:100) S.R.W.	Severe anaphylaxis

*S.R.W., short ragweed pollen extract.

presence of egg antigen in these dusts appeared in a separate series of preliminary trials dealing with the effect of injecting various volumes and concentrations of dust extracts in control animals. Severe anaphylaxis occurred unaccountably among the progeny of egg-sensitized females when injected for the first time with dust extracts.

Animals for the tests recorded in Table IX were progeny of guinea pigs maintained in a colony of breeding stock, none of which had been used for sensitization studies. The possibility of unintentional sensitization to egg antigen was rigorously excluded during the breeding and maintenance of the guinea pigs and in the manipulations of preparation and administration of house dust extracts.

HOUSE DUST AND RAGWEED POLLEN

Short ragweed pollen antigen was not detected in the house dust extracts. (Table X.)

DISCUSSION

Development of a satisfactory technique for sensitizing guinea pigs to water extracts of cotton linters and house dusts has enabled investigation of their antigenic components.

Water-soluble antigens of linters (seed hairs) and kernel (embryo) of cottonseed have been shown to be dissimilar. Samples of cotton linters representing high and low grades were free from antigens of the kernel. When the structure of the seed coat and the mechanics of the delinting process are examined, the possibility of contamination of linters with antigenic material from the seed kernel appears to be of minor significance. Relevant to the matter of contamination, however, is the fact that cottonseed is exposed to and accumulates a variety of extraneous substances in the course of maturing in the field, harvesting, ginning, and storage.

In the experiments reported the effect of age upon the antigenic properties of the linters was not investigated. The lower antigenicity of sample AI#35, as compared with that of samples AI#1 and AI#7, coincides with the observations of Cohen and his co-workers,[7] but data available did not permit evaluation of age as a factor influencing antigenicity of the linters used.

House dusts from three sources differed significantly in antigenic potency. In these dusts antigens common to cotton linters and egg white were identified. Wool antigen was demonstrated in two of them.

A nonspecific toxic factor in house dust extracts previously reported[2] was not completely removed by prolonged dialysis of the dust extracts. Anaphylactoid symptoms induced by this toxic factor can be differentiated from symptoms of anaphylaxis by inclusion of adequate controls.

Concentration of linters extracts to increase their antigenic potency led to recognition of a nonspecific toxic factor different from that of

house dust extracts. Control animals receiving intravenously 2 ml. of the concentrated linters extracts exhibited symptoms of toxicity which appeared thirty or more minutes after the injection. Symptoms were a staring coat, diminished activity, and absence of normal response to noise or handling. If not forced to move, the animals remained motionless in a crouched position for several hours. Complete recovery from these symptoms was noted in examination of the animals on the day following the injection. Intravenous injection of linters extract of tenfold concentration caused an immediate prostration and death in a few animals of from 350 to 400 Gm. body weight. Generally, the immediate prostration was followed by rapid partial recovery to a condition similar to that with delayed symptoms resulting from the smaller doses.

According to several investigators,[8-11] dialysis does not remove the allergenic components of house dust extracts, but it does eliminate color and other extraneous and presumably undesirable constituents. Evidence presented in this report indicates that the major portion of the antigenic components of the house dust extracts was retained by a cellophane membrane during prolonged dialysis, but some dust antigen was also demonstrated in the dialysates.

SUMMARY

Water-soluble antigens of cotton linters and cottonseed kernel are dissimilar and readily distinguishable by the technique described.

House dusts from three sources contained an antigen common to cotton linters of grades commonly used in household furnishings and in manufacture of cellulose products.

Presence in house dust extracts of a nonspecific toxic factor which induced anaphylactoid symptoms after intravenous administration to normal guinea pigs is confirmed. This factor was detected in undialyzed extracts, dialyzed extracts, and in dialysates.

Extracts of cotton linters, concentrated in the manner described, may induce symptoms of distress and prostration terminating with death or delayed recovery when injected intravenously into normal guinea pigs.

Samples of house dust from different sources have been shown to be variable and complex with respect to antigen content, containing antigens identified with cotton linters, egg white, and wool. It has not been possible to demonstrate the existence of a single characteristic antigenic entity in house dust.

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ELECTROLYTE AND WATER EXCHANGE IN BRONCHIAL ASTHMA, WITH EMPHASIS ON THE INFLUENCE OF PITRESSIN*

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DURING the course of studies[1] on a group of children with persistent bronchial asthma, it was observed that certain changes in the electrolyte and water balance were associated with definite variations in the degree of asthma. Placing the patients on a special low mineral, acid-ash diet which induced a low water retention with an accompanying loss in weight improved the asthmatic condition, and the introduction of artificial fever after the children had been on the low salt regimen for a short period of time often led to a complete disappearance of the asthmatic symptoms. The remissions brought about by these procedures could be terminated by adding sodium chloride to the special diet or returning the patients to the general diet of the hospital which was without salt restriction. There was then an increase in water retention and a gain in body weight. During the periods when the children received the relatively high salt intake with water ad libitum, fever therapy was unable to produce any consistent favorable influence on the asthma. These observations suggested the desirability of examining more critically the relationship between the electrolyte and water balance in the mechanism of asthmatic attacks.[2]

Starling and Verney,[3] Manchester,[4] and McQuarrie and Peeler[5] have shown that pitressin, the antidiuretic principle of the pituitary gland, causes a retention of body water, with a coinciding absolute increase in the output of sodium and chloride. If the water intake is relatively high and the sodium chloride intake is very low during a period of sustained pituitary antidiuresis, body water is retained without the storage of sodium chloride. This phenomenon offers a unique opportunity to dissociate the effects of water and salt in the asthmatic patient. The following investigation was therefore undertaken.

MATERIALS AND METHODS

Six children selected on the basis of severity and intractability of their asthmatic attacks were placed under constant environmental conditions in the hospital. The subjects ranged from 5 to 16 years in age. Only one child was under observation at one time. At such time he was under the constant supervision of nurses carefully instructed in his care, who weighed him daily under uniform conditions on scales sensitive to

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5 Gm., collected the urine as twenty-four-hour specimens, measured and preserved it for future chemical analyses, and made certain that the diet and medications were taken exactly as ordered.

Only one diet was employed during the special periods of study. It consisted of egg yolk, 105 Gm.; 35 per cent cream, 105 Gm.; clear lemon juice, 63 Gm.; pure cane sugar, 193 Gm.; and distilled water 600 Gm. The formula contained protein, 18.87 Gm.; fat, 77.0 Gm.; and carbohydrate, 201.99 Gm. The important mineral constituents were as follows: Na, 0.12 Gm.; K, 0.33 Gm.; and Cl, 0.18 Gm. The children daily were given four evenly spaced feedings of this formula which had reasonably adequate basal dietary constituents, but an extremely low sodium content. The amount of the feeding weighed out for each meal depended upon the initial weight of the patient. Calculated daily intake of sodium was from 120 to 700 mg. Vitamin requirements could be met by using vi-penta perles (Roche) containing vitamins A, B_1, B_2 (G), C, and D. Distilled water was given at equally spaced intervals, 400 c.c. per day during control periods and from 1,200 to 2,000 c.c. per day during antidiuretic sessions.

The studies were conducted in the following manner. An initial control period accustomed the patients to the extremely low salt regimen and established the frequency and severity of the asthmatic attacks. Then, while the low salt intake was maintained, the water intake was increased, and pitressin or the solution containing the pressor principle of the posterior lobe of the pituitary body relatively free from the oxytocic substance was administered by hypodermic injections in doses of from 0.2 to 0.5 c.c. every three hours, day and night. The procedure was able to sustain antidiuresis over a considerable period of time. After from twenty-four to thirty-six hours, during which time the weight increased, due to retained water, 2 to 5 per cent of the initial body weight, the extra water and pitressin were stopped. This resulted after approximately six hours in a copious diuresis, the patients usually reaching a new weight level below the initial figure.

Modifications of the antidiuretic routine just described were made several times. The extra water given during the pitressin sessions was greatly reduced in some cases and entirely eliminated in others. The water allowed with the formula during the control periods was then added to the formula, and the combination was fed to the patients in equal portions every three hours. With this feeding schedule, the pitressin was administered for a longer period of time, namely, thirty-six to seventy-two hours.

Hourly observations of the children's conditions were made during the periods of study. The amount or degree of asthma was tabulated by using a code of arbitrary units. (See Table I.)

Specimens of blood were obtained from a few patients before, during, and after the administration of the pitressin. These were analyzed by

the following chemical methods: potassium, Shohl and Bennett;[6] chloride, Wilson and Ball;[7] and sodium, Butler and Tuthill.[8]

RESULTS

Although quite a number of children with persistent asthma were given the antidiuretic regimen, all of them did not respond satisfactorily. Some refused to take the extremely low sodium chloride diet consistently; others were unable to tolerate the pitressin. Repeatedly in these children the hormone would cause vomiting, cramps, and diarrhea, with an aggravation of the asthma. Six children cooperated well. A total of twenty studies was made on them. Usually, large amounts of extra water were given and the pitressin was administered for from twenty-four to thirty-six hours. Occasionally little or no extra water was employed, and the hormone was continued for from thirty-six to seventy-two hours.

Chart 1 reveals the data obtained during three investigations on two children. The first study was made on a 10-year-old girl who had a mild, but persistent, form of asthma. She was admitted to the hospital and placed on the low mineral, acid-ash diet, receiving daily 1,000 c.c. of the special diet or formula and 400 c.c. of distilled water. She was watched closely day and night by one of us (M. M. C.). For seven days the child stayed more or less quiet, and there was little change in the asthma. The weight remained practically constant. On the eighth day, pitressin was administered, and at the same time the water intake was increased by 1,200 c.c. After twenty-four hours of the antidiuretic regimen, the asthma suddenly disappeared. The pitressin and extra water were continued for twelve hours longer, at the end of which time the patient had gained 1.5 kg.

With the discontinuance of the pitressin, the urinary output began to increase rapidly. In fact, in twelve hours' time, 2,000 c.c. of urine was excreted with the result that the patient's weight dropped to a figure 0.5 kg. below that of the control period. Despite loss of body fluid, the asthma did not return. The diuretic phase was followed by a final period of observation during which the patient continued to receive the formula with a small amount of water. The weight of the child gradually returned to that of the initial period of observation. No asthmatic symptoms were apparent.

The child of the first study was permitted gradually to have more and more food. Eventually, however, after a few months, the sodium chloride content of the diet became too high, and asthmatic symptoms appeared. These increased in severity until the patient was again admitted to the hospital. After three days of rest, with the patient on the general diet of the hospital, the second study was started. She was placed on the low sodium chloride, acid-ash formula with a measured amount of distilled water. The asthma did not improve. Pitressin was then administered with only a small amount of extra water.

Twenty-four hours later the asthma had greatly improved, the antidiuretic effect having taken place at once, with a gain in body weight. The pitressin was continued for twelve more hours until all asthmatic symptoms disappeared. There was no recurrence during the diuretic and subsequent periods of observations.

The third study (Chart 1) was made on a 12-year-old boy with intractable asthma. Immediately on admission to the hospital, the child was placed on the special low sodium chloride formula with a measured amount of extra distilled water. However, the asthmatic symptoms increased in severity. On the eighth hospital day, pitressin was started and was continued for three days. During this time the patient excreted little urine and gained 1.5 kg. in weight. At the end of the three days, improvement in the asthma was noticeable.

After the pitressin was stopped, diuresis started at once and continued for two days, with the result that the child lost 2 kg. in weight. At the end of the diuretic phase, the asthmatic symptoms completely disappeared, but in a few days there was evidence of a return of the asthma. The pitressin was immediately administered for another three-day period, with a resulting marked retention of water. The asthma was aborted. The antidiuretic period was accompanied by another increase in weight, to be followed by a 2 kg. loss during the diuretic phase. However, in the subsequent period, the weight of the patient returned to that at the time of admission to the hospital. There was no recurrence of asthmatic symptoms.

During the second and third studies, the levels of some of the serum electrolytes were obtained. Specimens of blood were drawn before, during, and after the administration of pitressin. These were analyzed for potassium, chloride, and sodium, and they showed that the antidiuretic phase was accompanied by a moderate drop in the serum electrolytes, followed by another fall in the levels after diuresis had started. Recovery took place quite rapidly during the subsequent and final periods, the serum potassium, chloride, and sodium all returning to the normal range. At the present time, we can attach no significance to the changes which have occurred in the blood electrolytes.

The three studies shown in Chart 1 represent fairly accurately the types of response to pitressin in the six subjects who submitted to a total of twenty observations. The results of these studies are interesting and encouraging. During the water retention phase of each observation, a reduction in the number and severity of asthmatic attacks occurred in eighteen instances, in seven of which there was complete cessation of symptoms. In one case the symptoms remained unchanged, and in another child who developed mild diarrhea a slight increase in symptoms occurred. During the diuretic phase, improvement in symptoms continued in nineteen instances, with complete remissions developing fourteen times. In the child who had diarrhea

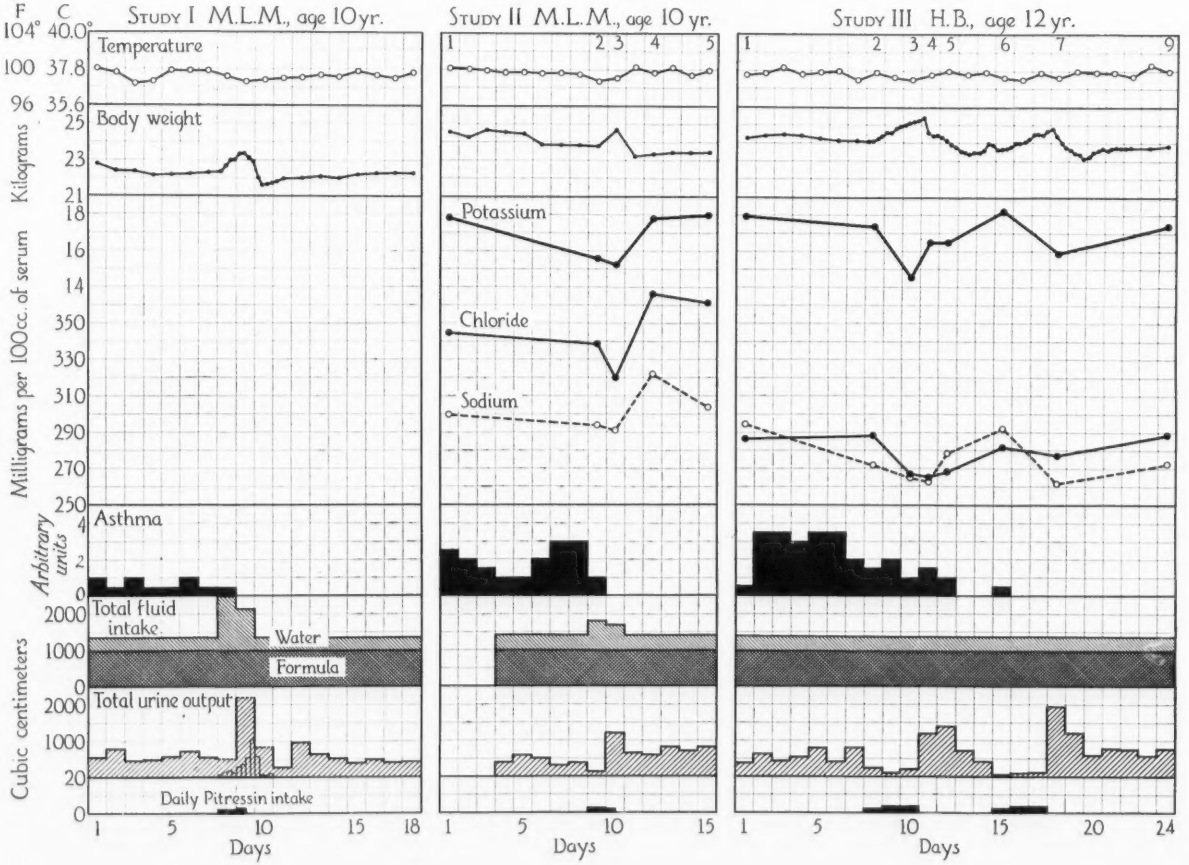

Chart 1.—Data obtained during three pitressin studies on two children with intractable bronchial asthma, showing the various types of response of the asthma to the hormone, the total dosage of the pitressin and the amount of extra water which varied in each case.

the asthma continued to be slightly aggravated during diuresis but improved during the subsequent period. Two other patients experienced improvement during the period following diuresis. In two instances symptoms recurred spontaneously at the end of the period of observation. The remainder of the patients continued to have remissions until upset by some extraneous factors. The results of the experiments are summarized in Table I.

TABLE I

INFLUENCE OF PITRESSIN ON TWENTY ATTACKS OF BRONCHIAL ASTHMA IN 6 CHILDREN

EXPERIMENT NUMBER	INTAKE (MG. PER DAY)		AMOUNT OF ASTHMA DURING VARIOUS PERIODS			
	NA	K	CONTROL	PITRESSIN	DIURESIS	SUBSEQUENT
1	120	360	1*	0*	0*	0*
2	200	600	3	0	0	0
3	200	2,100	3	0	0	0
4	200	2,100	3	1	0	0
5	200	2,100	2	1	0	0
6	500	1,500	3	1	0	0
7	500	1,500	1	0	0	0
8	200	600	4	2	0	0
9	120	360	4	1	1	3
10	120	360	4	1	1	2
11	120	360	4	2	2	0
12	120	360	1	0	0	0
13	120	360	4	2	0	0
14	120	360	2	1	0	0
15	700	2,000	4	2	1	1
16	700	2,000	3	3	2	1
17	500	1,500	2	0	0	0
18	200	600	3	0	0	0
19	200	600	2	3†	4†	1
20	200	600	4	1	0	0

*The numbers represent the amount or degree of asthma in arbitrary units as follows:

0, No asthmatic wheezing observed and no epinephrine used.

1, Wheezing present for at least one hour a day, requiring one dose of epinephrine.

2, Wheezing lasting three hours a day, requiring usually three doses of epinephrine.

3, Wheezing present about half the time or at least twelve hours a day, requiring about five doses of epinephrine a day.

4, Continuous wheezing, requiring eight or more doses of epinephrine a day.

†Mild diarrhea was present during these periods and the asthma was temporarily aggravated.

COMMENT

It would appear from the foregoing observations that bronchial asthma can be influenced favorably by the administration of the antidiuretic principle of the posterior lobe of the pituitary gland. This hormone was discovered by Kamm[9] in 1928 and called pitressin. Since that time many experiments have been carried out and much has been written concerning its effects in animals and in man. In man, the three most important are: first, the stimulation of intestinal peristalsis; second, the pressor influence on the cardiovascular system; and third, the reduction of kidney excretion.[10]

Some of the children did have gastrointestinal reactions following the administration of pitressin. In most of these cases there was epigastric distress and nausea. In a few cases this was followed by marked vomiting and diarrhea and an immediate aggravation of asthma so that the hormone had to be discontinued at once. In the majority of these children, the reaction occurred with each attempt to use the pitressin. This seemed to indicate existence of an idiosynerasy to the hormone. In a few instances, there was a relatively mild intestinal upset. After twelve hours, however, improvement was sufficient to permit a continuation of the pitressin as long as necessary.

Although many diverse effects have been reported in animals, there was little change in blood pressure in our patients while they received pitressin. The blood pressure did rise slightly after an injection of the hormone, but the elevation was transient. There was no consistent change in the pulse rate. No alarming changes in blood pressure or pulse rate occurred as long as pitressin was employed in doses just large enough to produce the antidiuretic effect.

The reduction in the excretion of urine, especially after the drinking of extra water, has been considered to be due to the direct action of the hormone on the renal mechanism. Shohl[11] states that part of the effect seems to be on the blood vessels of the kidney rather than on the nervous control, for antidiuresis is evidenced even after the severing of all the kidney nerves. Some observers believe that primarily pitressin affects the other tissues of the body and that the kidneys function in a purely secondary manner in response to changes in the blood circulating through them. According to McQuarrie,[12] the action is a complicated one involving both the kidneys and the general body tissues simultaneously. The first response to the hormone is constriction of the efferent glomerular vessels which produces a temporary diuresis, while a later, more striking response is constriction of the afferent vessels which results in antidiuresis.[13] Geiling,[14] however, reports that increased reabsorption from the kidney tubules resulting from a specific effect of the pitressin on the tubular epithelium may be largely responsible for the antidiuresis. The loop of Henle may be the chief site of the antidiuretic action in the kidney.[11]

The work of Stehle[15] is most often quoted to suggest that the antidiuretic qualities of extracts of the posterior lobe of the pituitary gland produce their effect by a direct action on the tissues of the body. Because he found an increased urinary excretion of various salts during antidiuresis, he concluded that the effect of the hormone was to mobilize electrolytes into the blood and thus permit the tissues to take up more water.

When a patient who has been on the low mineral, acid-ash diet for a short period of time is made to retain from 2 to 5 per cent of his original body weight by the administration of pitressin and the addition of distilled water to his diet, a significant decrease in the total

osmolar concentration of the electrolytes in the extracellular body fluid occurs. There is a strong tendency for an excess of water to enter the fixed tissue cells and for the intracellular elements to diffuse outward because of the lowered osmotic pressure of the fluid outside of the cells.[16] This arrangement permits the storage of water in the body without the development of any edema.

Among the elements involved in the changes which occur during pitressin antidiuresis are potassium and sodium. Potassium passes from the cells into the extracellular spaces favoring the retention of the extra water. Sodium, on the other hand, leaves the interstitial fluid to enter the blood plasma and is excreted in fairly large amounts as sodium chloride in the urine. The excretion of the salt continues to a lesser extent during the diuretic phase.[17, 18]

With the subject on an extremely low sodium chloride diet, loss of salt during and after the administration of pitressin leads to a rather marked depletion of sodium chloride in the body. This apparently has a favorable influence on the asthma.[19] The presence of the large amounts of stored water during the antidiuretic period or its loss during the diuretic phase has little effect. The asthma improves soon after the pitressin therapy is started, when the patient is retaining water and excreting a small amount of urine with a relatively high sodium chloride content. Improvement continues after the pitressin has been discontinued, at which time the subject is losing much water with more sodium chloride, a fact which will be reported in detail in a future communication.

The rather sudden favorable response of the asthma in some cases to the pressor hormone of the posterior lobe of the pituitary gland has brought up the question as to whether the pitressin has a more or less direct action upon the asthmatic mechanism. The dyspnea of asthma is considered to be due to a stenosis of the bronchi or bronchioles produced by a spasm or constriction of the bronchial musculature and a congestion of the mucous membranes or edema of the bronchial wall. Epinephrine relaxes the muscles of the bronchi, and Bischoff and Long[20] have reported that certain effects of pitressin, when they occur, resemble almost exactly the effects produced by adrenalin, notably the rise in the blood pressure, blood sugar, and blood lactic acid. They are tempted to account for these changes on the basis that the hormone stimulates the release of epinephine. Enough of the adrenalin might be liberated to produce a relaxation of the bronchial musculature during an asthmatic attack.

The bronchial wall congestion is often accompanied by the secretion of much mucus into the lumen of the bronchi and the formation of mucus plugs which may interfere greatly with the passage of air and lead to rather severe paroxysm of dyspnea. Anything which might reduce the mucus in the bronchial lumen would decrease, to a great

extent, the severity of the asthma. Pitressin could be considered to do this since there is proof that the hormone inhibits salivary, gastric, and intestinal secretions, and bronchial secretion, therefore, might also be depressed.[14, 21] However, further investigations to determine the exact nature of the beneficial effect of pitressin in bronchial asthma are necessary, and they are now in progress.

SUMMARY

In a previous communication, the authors have presented evidence which indicated that various procedures inducing electrolyte and water changes in the body had a definite influence upon persistent bronchial asthma. An extremely low sodium chloride diet improved the asthmatic conditions, and fever therapy then led to remissions.

The remissions were terminated by the ingestion of sodium chloride. During the periods of increased salt intake, the subject drank more water, stored much of it, and gained weight. The question therefore arose as to whether the increased water storage or the extra salt was instrumental in precipitating the asthmatic symptoms.

The action of the pressor principle of the posterior lobe of the pituitary gland offers an answer to this question. This hormone, pitressin, when injected subcutaneously, causes a retention of body fluids without the aid of an increase in body salts.

Many asthmatic children were given pitressin, and six of them with intractable asthma who tolerated the hormone were subjected to special studies. A total of twenty observations were made; three of the most typical studies are presented graphically on a chart.

The subjects were all placed on an extremely low sodium chloride diet, and when pitressin was administered, there was a retention of water up to 2 kg. in some of the patients. Improvement in the asthma began during the antidiuretic phase and continued through the diuretic and subsequent periods, proving that the storage of large amounts of water in the body and its sudden loss had apparently little influence on the asthmatic symptoms.

A review of the literature discloses investigations which indicate that, during pitressin antidiuresis and diuresis, despite low salt intake, sodium chloride is excreted, leading to a marked loss of body salt.

It is apparent that bronchial asthma can be ameliorated, even in the presence of excessive hydration, if there is an associated depletion of sodium chloride.

No positive therapeutic implications are warranted at this time, since the procedures outlined in this communication may still be considered rather involved and technically difficult to carry out with effective exactness. The whole subject is, therefore, of value more as an investigative tool rather than a therapeutic procedure.

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NOTE ON THE SERUM SODIUM CONCENTRATIONS OF ALLERGIC AND NONALLERGIC PERSONS

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THE present report gives the results of a comparison of the serum sodium concentrations of fifty persons who were suffering from more or less severe attacks of asthma, urticaria, or allergic rhinitis, with those of 133 persons who gave no personal or family history of allergy. This latter group included thirty normal persons, thirty-five women in the first half of pregnancy, and sixty-eight ambulatory patients with symptoms of chronic diseases other than allergy.

The serum sodium concentrations of these allergic and nonallergic persons were determined in duplicate by a modification of the method of Butler and Tuthill.[1] The averages of the duplicate determinations, expressed in milligrams per cent, have been recorded in Table I. None

TABLE I

SERUM SODIUM CONCENTRATIONS OF ALLERGIC AND NONALLERGIC PERSONS

CLASSIFICATION	NUMBER OF CASES	NUMBER OF DETERMINATIONS	RANGE	MEAN	VARIATION OF MEAN FROM NORMAL	STANDARD ERROR OF DIFFERENCE*
Normal	30	30	314-340	326.5	–	–
Nonallergic						
Pregnancy	35	35	303-331	319.5	+7.0	1.48
Chronic inflammation	24	24	303-351	329.0	–2.5	2.61
					–2.9	3.01
Cardiovascular	18	18	312-350	329.4		
Hypothyroidism	17	17	310-342	330.2	–3.7	2.34
Hyperthyroidism	9	9	307-336	323.8	+2.7	3.33
Total	103	103	303-351	325.8	+0.7	1.68
Allergic						
Allergic rhinitis	30	40	307-347	327.7	–1.2	1.93
Asthma	10	18	310-343	325.1	+1.4	2.34
Urticaria	10	12	318-347	328.0	–1.5	2.57
Total	50	70	307-347	327.0	–0.5	1.48

All values expressed in milligrams per cent.

*According to Fisher,[6] the difference between the means must be twice as great as its standard error to be significant.

of these concentrations fall outside the limits of reported normal values.[2, 3] Moreover, a statistical analysis of the data indicates that none of the groups of concentrations, except those of the pregnant women, differs significantly from the present normal group.

The concentrations of the pregnant women are significantly lower than those of the present normal group, a fact probably accounted for

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by the hydremic plethora of pregnancy. These low concentrations are especially interesting since pregnancy is known frequently to reduce the severity of allergic manifestations, and they suggest that retention of water without sodium reduces the severity of allergic manifestations in pregnancy just as it reduces the severity of asthmatic symptoms in some of the patients treated with pitressin by Cooke and Stoesser.[4]

This suggestion of a correlation between the severity of allergic symptoms and serum sodium concentrations was not borne out in the present study, however, since repeated observations during the treatment of several of the patients revealed no evidence of a direct connection between the serum sodium concentrations and either the type or the severity of the allergic manifestations. On the contrary, our observations tend to confirm and extend the observation of Sheldon, Howes, and Stuart[5] that the metabolism of water parallels that of sodium in asthmatic (and other allergic) attacks. It is possible, of course, that some other factor masked what would otherwise have been a significant change in serum sodium concentration, but an analysis of the data reveals no correlation between the serum sodium concentrations and such variables as age, diet, race, or sex.

SUMMARY

A comparison of the serum sodium concentrations of fifty allergic and 133 nonallergic persons has revealed no evidence of a direct connection between the allergic symptoms and the concentration of sodium in the sera of the allergic patients.

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A STUDY IN FOOD ALLERGY

The Relationship Between the Allergic Activity and the Protein Fractionization of Selected Foods*

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THE following investigation was undertaken for the purpose of studying and determining the chemical nature of a few of the food substances commonly found to be allergens or generators of allergy in man. The importance of studies of this nature will be appreciated when it is known that 35 per cent of the students entering the University of Michigan each year are found to be allergic[1] and that it is believed that from 7 to 10 per cent of the general population is in some way handicapped by this constitutional state,[2] whether hereditary or acquired.

The chemical nature of allergens is not well understood. Various investigators have reported evidence to show that pollen allergens are protein. The food allergens seldom have been studied in this respect.

The necessity of standardizing protein extracts is recognized. The statement is made by Black[3] that two different batches of pollen, obtained from the same source and prepared by the same technique, varied 62½ times in potency. During the past few years many workers have standardized their extracts to the protein nitrogen or total nitrogen content. Cowie and Wardell[4] standardized over 100 allergens to 5 mg. per cent total nitrogen, and they obtained satisfactory and comparable reactions without inducing marked local or general reactions such as frequently occur with unstandardized preparations. The variation of protein nitrogen content in the same type of pollen collected in different seasons was pointed out by Cooke and Stull.[5] However, they found that, when they diluted their extracts on the basis of protein nitrogen content, the ability to induce skin reactions was the same.

With these considerations in mind, the following foods were selected as representative allergens for study: the banana (*Musa sapientum* L.), the white bean (*Phaseolus vulgaris* L.), and the white potato (*Solanum tuberosum* L.).

LABORATORY PROCEDURES

Extraction of Proteins From Fresh Foods.†—The three foods being investigated were first crushed by the following methods: the ripe

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From the Department of Pediatrics and Infectious Diseases of the University of Michigan.

†Aseptic technique was used in the preparation and handling of the fresh foods. All instruments and apparatus were sterilized before use. As a further safeguard, a preservative was used in the extraction of the foods. During the precipitation and purification of the proteins, as well as in their extraction, chemical and bacteriologic contamination was avoided by using the utmost care. The extracts were preserved with 0.1 per cent nipagin, as recommended by Fenton,[6] which was added to the extracting fluids before using them. The extracts were standardized and then bottled under sterile precautions.

bananas were peeled and cut into large pieces; the beans were washed with water to remove any adherent foreign particles, and then ground in a mortar; the potatoes were scrubbed and ground in a meat grinder. After this preliminary preparation, the foods were placed in several liter extraction bottles, 2 per cent sodium chloride was added, and the mixtures were subjected to violent shaking until the foods were emulsified, after which the bottles were shaken intermittently for forty-eight hours. After forty-eight hours the contents were filtered through a fine filter paper* to separate the sodium chloride-soluble proteins from those not soluble in this reagent. The residue of each food (after removal of the sodium chloride-soluble proteins) was then extracted for forty-eight hours with 2 per cent sodium hydroxide and filtered, the filtrate containing the alkali-soluble metaproteins. Excess ammonium sulfate was added to the combined filtrates (the sodium chloride and sodium hydroxide extraction of each food) to salt out the proteins. The precipitated proteins were removed by filtration and dialyzed in a collodion membrane to remove the ammonium sulfate. Distilled water flowing at the rate of 40 liters per twenty-four hours was used for dialyzing. The dialysate was tested every six hours with Nessler's solution, until all traces of ammonium sulfate were removed.

The collodion sacs containing the proteins were removed, fastened on a wire line, and allowed to dry for approximately seventy-two hours at room temperature. Then the semidry contents of the sacs were transferred to open Petri dishes† and placed in an electric oven at 50° C. for six hours. This material remained over night in the oven as it gradually cooled to room temperature. The following morning these dried proteins were powdered and stored in airtight glass-stoppered bottles until used for separation of various protein fractions.

Separation of Protein Fractions.—The protein fractions of each food were separated on the basis of solubility. First the water-soluble albumin and proteose were removed. The dried proteins prepared by the method described were weighed in sterile flasks. One cubic centimeter of triple distilled water was added for each 10 mg. of protein. The flasks were stoppered with sterile rubber stoppers and shaken rapidly for several minutes to thoroughly wet the protein. The extraction was then continued for forty-eight hours at room temperature, during which time the flasks were slowly shaken intermittently. After filtration the residue was re-extracted twice with water to attempt complete removal of all water-soluble proteins, as any remaining would be soluble in sodium chloride, producing erroneous results. This residue was then extracted, three times with 0.85 per cent sodium chloride to obtain the proteins soluble in this reagent and not soluble in water. The

*Sterile Whatman's No. 42 filter paper in sterile funnels was used for all filtration of all proteins.

†The depth of the protein in the dishes was not more than 1 cm.

alkali-soluble proteins were removed from the residue of the previous extraction with 0.2 per cent sodium hydroxide. The proteose was separated from the albumin by heating part of the water-soluble fraction in a boiling water bath for ten minutes, then filtering to remove the coagulated albumin, retaining the heat-stable proteose in the filtrate. The Molisch, Millon, and biuret tests were made on every protein extraction. The total nitrogen and nonprotein nitrogen were determined.

Dried proteins of banana, bean, and potato were obtained from a chemical company. These proteins were extracted with 0.85 per cent sodium chloride for forty-eight hours at room temperature.

*Preparation of Collodion Membranes.**—The collodion membranes used for dialysis and ultrafiltration were made with 9 per cent refined pyroxylin dissolved in an ether-alcohol mixture (60 per cent ether with 40 per cent alcohol). When the pyroxylin was completely dissolved, 5 per cent ethylene glycol was added to toughen the membranes[7] which were molded in test tubes or flasks and dried beneath a large Bell jar. The pore size was determined by the drying time, for it is known that the longer the time of drying, the smaller the pores. The period of drying can be terminated by immersing the container with the membrane in distilled water or in a water-alcohol mixture.

Removal of Proteins by Ultrafiltration.—Twenty-five cubic centimeters of each protein extract was ultrafiltered through a collodion membrane with the aid of a suction pump. Approximately one-half the amount was allowed to filter through the collodion sac. This filtrate gave a negative Millon and biuret test.

Clinical Testing With the Various Extracts.—The following extracts were used for intradermal testing in normal and allergic students:

1. The water-soluble, sodium chloride-soluble, and sodium hydroxide-soluble fractions of proteins prepared from banana, bean, and potato.
2. The heated (boiling water bath for ten minutes) water-soluble fraction of these three foods containing proteose.
3. The sodium chloride-soluble (including water-soluble) fraction of the proteins of these three foods obtained from a chemical supply company.
4. The ultrafiltrates and the emulsions of the various extracts, purposely allowed to remain in the collodion sacs.

All extracts containing more than 5 mg. per cent total nitrogen were standardized to this amount.

The tables record the results obtained.

RESULTS OF CLINICAL TESTS

Each extract used in this investigation was injected intradermally into the author's skin before it was used on any other patient, he being

*I am indebted to Dr. H. G. Smith of the Department of Pharmacology of the University of Michigan for information concerning the preparation of these membranes.

TABLE I

NITROGEN CONTENT OF EXTRACTS OF BANANA, BEAN, AND POTATO PROTEIN*

	EXTRACTED WITH 0.85% NaCl (TOTAL NITROGEN %)	NaCl EXTRACTION AFTER ULTRAFILTRATION	
		EXTRACT RETAINED IN COLLODION SAC (TOTAL NITROGEN %)	FILTRATE PASSED THROUGH COLLODION SAC (TOTAL NITROGEN %)
Banana	14.7 mg.	15.9 mg.	11.0 mg.
Bean	8.1 mg.	15.4 mg.	10.8 mg.
Potato	4.8 mg.	6.3 mg.	3.7 mg.

*Dry proteins obtained from a chemical supply company. These proteins extracted with sodium chloride contained the water-soluble, as well as the sodium chloride-soluble, proteins.

TABLE II

NITROGEN CONTENT OF PROTEIN FRACTIONS OF BANANA, BEAN, AND POTATO*

PROTEIN FRACTIONS	TOTAL NITROGEN (MG. %)	TOTAL NITROGEN AFTER ULTRAFILTRATION	
		EXTRACT RETAINED IN COLLODION SAC (MG. %)	FILTRATE PASSED THROUGH COLLODION SAC (MG. %)
Banana			
Water-soluble	15.1	28.3	4.7
Sodium chloride-soluble	4.4	4.5	2.6
Sodium hydroxide-soluble	77.8	–	–
Bean			
Water-soluble	4.7	4.8	3.8
Sodium chloride-soluble	3.6	2.7	1.5
Sodium hydroxide-soluble	122.0	–	–
Potato			
Water-soluble	7.9	8.9	6.8
Sodium chloride-soluble	6.1	4.4	3.7
Sodium hydroxide-soluble	102.0	–	–

*Proteins prepared from fresh foods.

a clinically nonallergic person; however, his skin reacted to three proteins when tested intradermally with 120 different allergens. Banana was one of these. The four allergic persons were student volunteers.*

The utmost care was used in cleaning and sterilizing the needles and Luer syringes. Tuberculin Luer syringes with 26 gauge needles were used. The amount of each extract injected was 0.03 c.c.*

The reactions were recorded by taking the average of the largest perpendicular diameters of the wheals and areas of redness. Measurements were made at fifteen and thirty minutes, and at one, two, six, and twenty-four hours after injection. The color of the reactions was recorded according to the degree of redness, as is used in this research laboratory and described by Cowie.[8] In order to save space, only the

*I wish to express my gratitude to Dr. B. Jimenez for securing the student volunteers, and to Dr. M. Fenton for testing the patients.

areas of redness for the thirty- and sixty-minute readings are recorded. For the sake of clearness, wheal measurements are omitted. For experimental work this laboratory requires a thirty-minute reaction or longer for acceptance as a positive test. A fifteen-minute reaction that is not sustained to the thirty-minute observation may not be positive.

An analysis of the intradermal reactions shows the following:

Reactions to Banana.—The otherwise nonallergic patient (John E.) reacted to the albumin fraction of the banana. The two allergic subjects (George S. and Carrol R.) gave marked reactions to all fractions. There were no reactions to the ultrafiltrates.

Reactions to Bean.—The nonallergic control (John E.) gave a very slight positive reaction to the globulin fraction of this food. One allergic patient (Mary B.) reacted to all fractions. The other patient (George S.) reacted to all except proteose, to which he was negative.

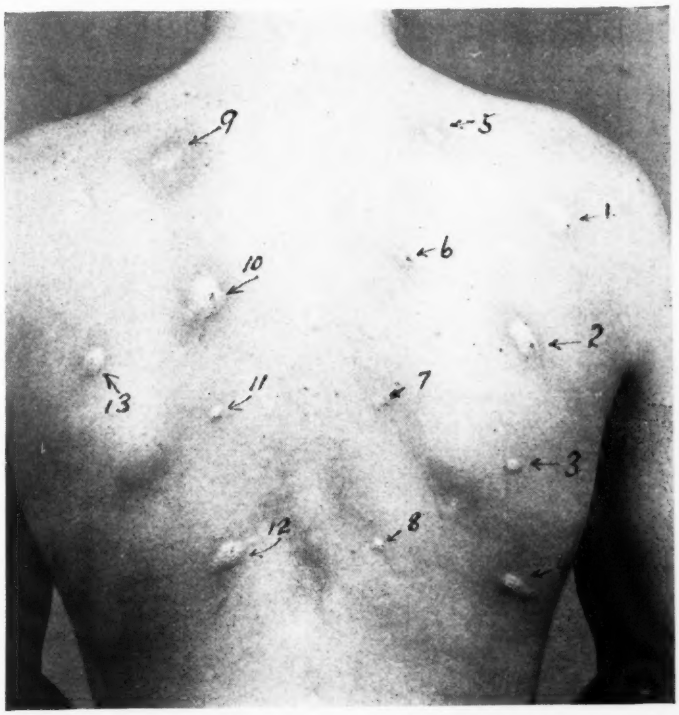

Fig. 1.—Reaction of allergic skin sensitive to banana proteins (George S.). The photograph was taken twenty-five minutes after the intradermal injection of various fractions of banana, and the reactions were measured five minutes after the photograph was taken (Tables II and III).

1, Sodium chloride extract of one banana protein obtained from a chemical supply company and containing albumin, proteose, and globulin; *2*, residue of above-described extract, after ultrafiltration; *3*, filtrate of this ultrafiltration; *4*, sodium chloride extract of banana protein, prepared from fresh bananas and containing globulin; *5*, residue after ultrafiltration of *4*; *6*, ultrafiltrate of *4*; *7*, sodium chloride control; *8*, water control; *9*, water extract of banana protein, prepared from ripe bananas and containing albumin and proteose; *10*, residue of *9*, after ultrafiltration; *11*, ultrafiltrate of *9*; *12*, water extract of *9* plus heat, containing proteose; *13*, sodium hydroxide extract of banana protein, prepared from ripe bananas and containing alkali metaprotein.

TABLE III

RESULTS OF THE INTRADERMAL INJECTION OF THE PROTEIN FRACTIONS OF BANANA, BEAN, AND POTATO EXTRACTS

PROTEIN FRACTION	SKIN REACTION					
	NONALLERGIC PATIENT		ALLERGIC PATIENTS			
	30 MIN.	60 MIN.	30 MIN.	60 MIN.	30 MIN.	60 MIN.
Banana	*John E.*		*George S.*		*Carrol R.*	
Water-soluble (Albumins and proteoses)	28 mm.*	0 mm.*	42 mm.*	0 mm.*	42 mm.*	20 mm.*
Water-soluble (heated)† (Proteoses)	0	0	28	18	49	25
Sodium chloride-soluble (Globulins)	0	0	41	20	46	9
Sodium chloride-soluble‡ (Including water-soluble)	0	0	41	20	68	31
Sodium hydroxide-soluble	0	0	32	0	52	16
0.85% sodium chloride (Control)	0	0	0	0	0	0
Sterile water (Control)	0	0	0	0	0	0
Bean	*John E.*		*George S.*		*Mary B.*	
Water-soluble (Albumins and proteoses)	0 mm.	0 mm.	0 mm.	0 mm.	24 mm.	14 mm.
Water-soluble (heated)† (Proteoses)	0	0	0	0	24	0
Sodium chloride-soluble (Globulins)	0	0	32	24	28	0
Sodium chloride-soluble‡ (Including water-soluble)	0	0	46	31	32	14
Sodium hydroxide-soluble	0	0	40	34	24	0
0.85% sodium chloride (Control)	0	0	0	0	0	0
Sterile water (Control)	0	0	0	0	0	0
POTATO	*John E.*		*William C.*		*Mary B.*	
Water-soluble (Albumins and proteoses)	0 mm.	0 mm.	41 mm.	34 mm.	18 mm.	17 mm.
Water-soluble (heated)† (Proteoses)	0	0	44	28	23	19
Sodium chloride-soluble (Globulins)	0	0	35	32	36	32
Sodium chloride-soluble‡ (Including water-soluble)	0	0	49	44	27	22
Sodium hydroxide-soluble	0	0	0	0	30	23
0.85% sodium chloride (Control)	0	0	0	0	0	0
Water control (Sterile, distilled)	0	0	0	0	0	0

*The average of the two greatest perpendicular measurements of the diameter of the lesion in millimeters.

†Extracts heated in a boiling water bath for ten minutes and filtered to separate the albumin from the proteose fraction.

‡These extracts were made from proteins obtained from a chemical supply company; all other extracts were made from the proteins extracted from fresh foods.

TABLE IV

COMPARATIVE RESULTS OF THE INTRADERMAL INJECTION OF THE VARIOUS PROTEIN AND OTHER FRACTIONS OF THE BANANA, BEAN, AND POTATO

(DEMONSTRATING THAT THE ALLERGEN CAN BE REMOVED BY A COLLODION MEMBRANE)

FOOD FRACTIONS	SKIN REACTIONS					
	NONALLERGIC PATIENT		ALLERGIC PATIENTS			
	30 MIN.	60 MIN.	30 MIN.	60 MIN.	30 MIN.	60 MIN.
Banana	*John E.*		*George S.*		*Carrol R.*	
Sodium chloride-soluble* (Including water-soluble)						
Ultrafiltration residue†	0	0	48 mm.	18 mm.	41 mm.	19 mm.
filtrate	0	0	0	0	0	0
Sodium chloride-soluble						
Ultrafiltration residue	0	0	25	0	36	0
filtrate	0	0	0	0	0	0
Water-soluble						
Ultrafiltration residue	16 mm.	12 mm.	46	20	52	20
filtrate	0	0	0	0	0	0
Bean	*John E.*		*George S.*		*Mary B.*	
Sodium chloride-soluble* (Including water-soluble)						
Ultrafiltration residue	0	0	42 mm.	25 mm.	27 mm.	14 mm.
filtrate	0	0	0	0	0	0
Sodium chloride-soluble						
Ultrafiltration residue	0	0	28	14	30	16
filtrate	0	0	0	0	0	0
Water-soluble						
Ultrafiltration residue	0	0	0	0	32	14
filtrate	0	0	0	0	0	0
Potato	*John E.*		*William C.*		*Mary B.*	
Sodium chloride-soluble* (Including water-soluble)						
Ultrafiltration residue	0	0	42 mm.	30 mm.	26 mm.	23 mm.
filtrate	0	0	0	0	0	0
Sodium chloride-soluble						
Ultrafiltration residue	0	0	21	19	20	16
filtrate	0	0	0	0	0	0
Water-soluble						
Ultrafiltration residue	0	0	38	32	30	24
filtrate	0	0	0	0	0	0

*Extracts made from proteins obtained from a chemical supply company; all other extracts made from the proteins salted out of the investigated foods.

†Contents in the collodion sac after subjected to a negative pressure.

Reactions to Potato.—The nonallergic control (John E.) did not react to any fraction. The two allergic patients (William C. and Mary B.) reacted to all of the fractions.

DISCUSSION

In this investigation proteins were prepared from three different foods. They were extracted from these foods and were salted out by ammonium sulfate, which was removed by dialysis. The emulsions made

from these proteins gave a negative Molisch test and a positive biuret and Millon test indicating the presence of the protein molecule.

To further study the nature of the active principle, the permeability of membranes to these allergens was investigated. The first membranes used for dialysis would not retain the active allergen or the protein molecule, and a considerable quantity of protein was contained in the ultrafiltrate, so much that it would be detected with chemical tests. After several months of experimentation, membranes were prepared that would remove the protein from an emulsion. Ultrafiltrates from these contained no antigenic substance that could be recognized by intradermal testing of the skin of an allergic patient. These results show that the antigenic property of the extracts of the foods examined resides within the protein fraction and that more than one fraction of each of the food proteins studied may induce a reaction in an allergic skin. In this connection it is of interest to note that there is a variation in the reactivity of the skin to the specific protein fractions in different allergic persons sensitized to the same food. For example, in one patient sensitive to bean, the albumin and proteose fractions gave a positive skin reaction, which in another bean-sensitive patient they did not. Another example of the specificity of food protein fractions was demonstrated when testing two patients sensitive to potato; one reacted to the sodium hydroxide-soluble metaprotein fraction, and the other did not. One may find persons sensitive to all fractions, as is illustrated by the cases of banana sensitization.

In separating the protein fractions on the basis of their solubility, more than 75 per cent of the total protein obtained from each food was an alkali-soluble metaprotein. When standardizing these metaproteins to 5 mg. per cent of total nitrogen it was necessary to dilute them approximately fifteen, twenty, and even twenty-four times. The greatest concentration of sodium hydroxide that was injected into the skin under these conditions was less than 0.015 per cent, which was determined to be nonirritating and incapable of producing a false reaction. It is shown that these diluted emulsions contain sufficient antigenic substance to induce a skin reaction in a sensitive patient. Since these experiments indicate that foods contain a high percentage of sodium hydroxide-soluble protein which is capable of causing a marked skin reaction in a sensitive person, it would seem important that further work be directed to the study of this fraction.

CONCLUSIONS

1. The allergens or skin-exciting substances of the banana, bean, or potato can be removed from a protein emulsion by ultrafiltration through a collodion membrane.

2. The ultrafiltrate when injected intradermally into a patient sensitive to the specific allergen will not cause a positive reaction; on the

contrary, the colloidal residue remaining in the collodion sac elicits a marked reaction.

3. The allergen in the colloidal residue is either a protein or an unknown substance that is in permanent combination with a protein.

4. The separation of the protein fractions of these foods can be accomplished on the basis of their solubility in different solvents.

5. More than one protein fraction of a food may be capable of causing a definite skin reaction in a sensitized patient.

6. A protein fraction of a food causing a definite skin reaction in one allergic patient may not cause a reaction in another patient sensitive to the same food.

I wish to acknowledge the advice given to me by Dr. D. M. Cowie, Professor of Pediatrics and Infectious Diseases at the University of Michigan.

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STUDIES ON THE COLLOIDAL GOLD PHENOMENA IN ALLERGY*

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ANDERSON[1] found a consistent difference from the normal in the colloidal gold curve obtained on the serum of allergic individuals. He conjectured that a lack of some protein factor in the allergic serum was responsible. Since the gold number was introduced by Zsigmondy,[2] a number of attempts have been made to use this method for diagnostic purposes. Lange[3] in 1912 succeeded in developing a method which could be applied to spinal fluid, enabling the diagnosis of syphilitic, paretic, and meningitic conditions to be made. Since then several attempts to obtain characteristic diagnostic reactions upon the blood serum have been made, none of them gaining wide attention. Svedberg[4] mentioned a colloidal gold reaction for the diagnosis of tetanus and described the advancement of the hypothesis that the reaction is due to an increase in the serum globulin. Chrometzka[5] in 1936 published a method for the diagnosis of tumors by the use of a gold sol reaction upon serum ultrafiltrates.

It may be pointed out that the gold reaction developed by Lange is not identical with the gold number determined by Zsigmondy. In his original determinations the latter used a sufficient quantity of electrolyte to completely precipitate the gold. In fact, from his definition, the gold number is the number of milligrams of a substance required to protect 10 c.c. of standard gold sol from the action of 1 c.c. of 10 per cent saline solution. One cubic centimeter of 10 per cent saline will almost instantly precipitate the gold if a protective substance is not present. In the Lange test, however, the electrolyte concentration is so small as to produce no visible effect upon the gold sol; that is, the control tube remains unchanged. It can be readily understood that the Zsigmondy reaction is based upon protective action, but it is difficult to understand the mechanism of the phenomena described by Lange. The literature reveals considerable investigative work, none of which is very illuminating. The studies of Wernicke and Modern,[6] who noted the shift from protective to precipitative action in ox serum upon dialysis, and those of Silber and Friese,[7] who found antigenic properties in gold sol, may be mentioned.

In this study we have determined the gold numbers of the sera of 13 allergic and 8 normal children, ranging in age from 4 to 14 years. Those individuals regarded as allergic were children who suffered from perennial rhinitis, and in some instances perennial rhinitis and bron-

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chial asthma. Each had a predominance of eosinophiles in the nasal smear and was proved to be clinically sensitive to foods or inhalants, or both. Those individuals regarded as normal were children whose personal and family histories were negative for manifestations of allergy. They showed no pathology in their nasal tracts, their nasal smears revealed no eosinophiles, their Schick and Mantoux tests were negative, and they were found to be free from other abnormalities upon careful clinical examination. These 8 normal controls were selected as the most normal from 30 children in whom we had no reason to suspect personal or family allergy.

As a basis for the gold number determinations we have endeavored to establish the fact that the protective action of the serum is due to the protein fraction, or more exactly that fraction precipitated by trichloracetic acid.

Upon completion of these determinations we have studied the Anderson phenomena from the standpoint of the Lange reaction, using saline concentrations which do not in themselves precipitate the gold sol.

EXPERIMENTAL

The gold used was made after the method of Levine.[8] It meets the requirements of Bray.[9] The usual precautions about glassware, water, etc., were strictly observed.

From the serum of a normal individual the lipoid fraction was extracted by a 1:3 ether-alcohol mixture. Two-tenths cubic centimeter of this filtered extract was added to each of ten tubes containing 5 c.c. gold sol. Five-hundredths cubic centimeter of 10 per cent saline was added to the first tube, 0.1 c.c. to the second, and so on to 0.9 c.c., increasing by 0.1 c.c. in each tube. A similar setup was used as the control, but it contained only alcohol-ether mixture instead of lipoid extract. Both experiment and control cleared in the same tube after twenty-four hours. The experiment was repeated using allergic serum with the same result.

The protein of a normal serum was precipitated by the use of trichloracetic acid. The filtrate was titrated with 0.1 normal sodium hydroxide, and a trichloracetic acid solution of the same strength was made up. The acid containing the protein-free filtrate was added in varying amounts to a series of ten tubes, each containing 5 c.c. gold sol. The control acid was added in the same amounts to another set of gold tubes. Both filtrate and acid cleared in the same tube after twenty-four hours. The experiment repeated upon an allergic serum gave the same result.

The gold number determinations were run in the following manner: The blood was collected, the serum separated and diluted 1:500 with redistilled water. The setup consisted of eleven tubes and a control. In the first tube was placed 0.05 c.c. 1:500 serum, 0.1 c.c. in the second,

0.2 c.c. in the third, etc. To the control tube was added 1 c.c. water. Ten cubic centimeters gold sol was then added to each tube and the tubes were shaken. One cubic centimeter of 10 per cent sodium chloride was then added. The entire procedure was completed within one hour after the blood was collected.

The readings were taken after twenty-four hours, the tube showing no visible color change being taken as the end point. The total serum protein was determined after the method of Greenberg[10] and upon this basis the gold number was calculated. Table I gives the results.

TABLE I

PATIENT	DIAGNOSIS	TOTAL PROTEIN GM. PER 100 C.C.	GOLD NUMBER
O312	Allergy	7.4	.133
N815	Allergy	6.2	.122
N691	Allergy	6.2	.099
N683	Allergy	6.7	.121
O98	Allergy	6.4	.115
A994	Allergy	6.3	.088
L645	Allergy	7.1	.128
D991	Allergy	5.8	.081
D620	Allergy	7.1	.099
L382	Allergy	6.0	.108
O252	Allergy	6.9	.069
C138	Allergy	6.6	.066
O555	Allergy	6.2	.112
O125	Normal	7.0	.098
M616	Normal	6.6	.066
M639	Normal	7.1	.099
O138	Normal	7.2	.115
O139	Normal	6.2	.038
N656	Normal	6.4	.128
N619	Normal	6.4	.089
N667	Normal	6.0	.120

SUMMARY

DIAGNOSIS	TOTAL CASES	AVERAGE PROTEIN	GOLD NUMBER			
			AVERAGE	RANGE		AVERAGE DIFFERENCE
Allergy	13	6.52	.102	.066	.133	±16
Normal	8	6.61	.094	.038	.128	±22

The standard Lange colloidal gold test was then run on the serum of the patients being investigated. Because of the difficulties in securing adequate return in out-patient work, several substitutions were effected in the original list. Our standard of selection, however, was maintained throughout. In addition to the use of 0.4 per cent saline as advocated by Lange, a setup containing redistilled water in place of the salt was run at the same time. The results after twenty-four hours, together with a comparison of their averages, are given in Table II.

TABLE II

PATIENTS	DIAGNOSIS	GOLD PRECIPITATION AT DILUTIONS INDICATED																					
		WATER											0.4% SALINE										
		1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	CONTROL	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	CONTROL
N815	Allergy	5	5	5	5	5	3	1	0	0	0	0	5	5	5	5	5	5	5	4	3	0	
N691	Allergy	5	5	5	5	5	5	1	0	0	0	0	5	5	5	5	5	5	5	4	3	0	
N683	Allergy	5	5	5	5	4	1	0	0	0	0	0	5	5	5	5	5	5	5	4	3	2	0
A994	Allergy	5	5	5	5	5	1	0	0	0	0	0	5	5	5	5	5	5	5	4	3	2	0
L645	Allergy	5	5	5	5	5	1	0	0	0	0	0	5	5	5	5	5	5	3	2	1	0	0
D911	Allergy	5	5	5	5	5	3	2	1	0	0	0	5	5	5	5	5	5	5	5	3	2	0
L382	Allergy	5	5	5	5	4	3	1	0	0	0	0	5	5	5	5	5	5	5	4	3	2	0
C138	Allergy	5	5	5	5	4	3	1	0	0	0	0	5	5	5	5	5	5	5	5	3	2	0
N353	Allergy	5	5	5	5	4	1	0	0	0	0	0	5	5	5	5	5	5	4	3	2	1	0
9771	Allergy	5	5	5	5	4	2	0	0	0	0	0	5	5	5	5	5	5	4	3	2	1	0
M932	Allergy	5	5	5	5	5	3	1	0	0	0	0	5	5	5	5	5	5	3	2	1	1	0
O513	Allergy	5	5	5	5	3	2	1	0	0	0	0	5	5	5	5	5	3	2	1	1	0	0
O57	Allergy	5	5	5	5	4	2	0	0	0	0	0	5	5	5	5	5	4	3	2	2	1	0
M616	Normal	5	5	5	5	5	5	2	1	0	0	0	5	5	5	5	5	5	5	3	2	0	
M639	Normal	5	5	5	5	5	1	0	0	0	0	0	5	5	5	5	5	5	5	4	2	1	0
O138	Normal	5	5	5	5	5	1	0	0	0	0	0	5	5	5	5	5	5	4	3	2	1	0
O139	Normal	5	5	5	5	4	2	1	0	0	0	0	5	5	5	5	5	5	5	3	2	1	0
N619	Normal	5	5	5	5	5	2	1	0	0	0	0	5	5	5	5	5	5	4	3	2	1	0
O194	Normal	5	5	5	5	5	4	2	1	0	0	0	5	5	5	5	5	5	5	4	3	2	0
D820	Normal	5	5	5	5	4	3	1	0	0	0	0	5	5	5	5	5	5	4	3	2	1	0
F410	Normal	5	5	5	5	4	2	0	0	0	0	0	5	5	5	5	5	4	4	3	2	1	0

SUMMARY

TOTAL PATIENTS	DIAGNOSIS	AVERAGE GOLD PRECIPITATION AT DILUTION INDICATED																					
		WATER											0.4% SALINE										
		1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	CONTROL	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	CONTROL
13	Allergy	5	5	5	5	4.4	2.3	0.6	0.1	0	0	0	5	5	5	5	5	4.8	4.2	3.5	2.5	1.5	0
8	Normal	5	5	5	5	4.6	2.5	0.9	0.3	0	0	0	5	5	5	5	5	4.9	4.5	3.5	2.3	1.3	0

Chart 1 shows the averages of the gold precipitation in each tube plotted against the log of the dilution in that tube. It will be noted that, while the curve obtained with water shows some tendency to assume a position which might indicate a slight difference between the two sera, the effect holds only for the averages and not throughout each determination.

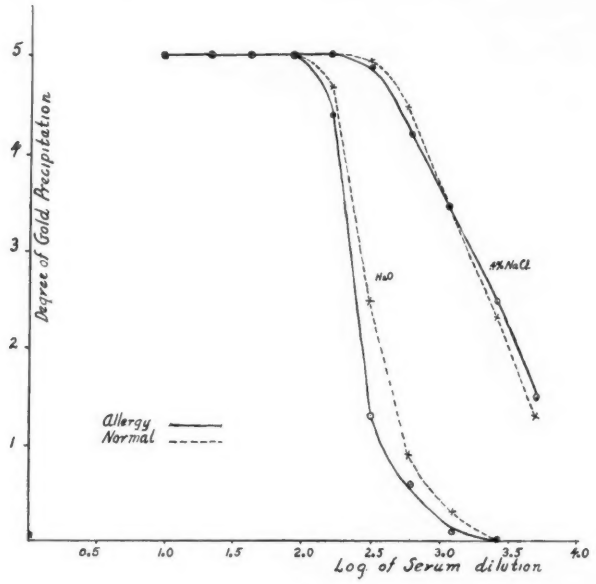

Chart 1.

SUMMARY

An attempt was made to show that the protective effect of blood serum on gold sol is due to the protein-like substances it contains, that is, those substances precipitated by trichloracetic acid.

Upon this basis gold number determinations were made on the sera of 13 allergic and 8 normal children, and the results were compared.

Lange tests, using both 0.4 per cent saline and redistilled water, were run on this series of patients, and the results were compared.

CONCLUSIONS

We found little difference in the gold numbers of the blood sera in this series of allergic and normal children.

The curves obtained by Lange determinations upon the blood sera of this series of allergic and normal children were similar, both in the 0.4 per cent and 0.0 per cent saline concentrations.

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THE FUTURE OF ALLERGY

PRESIDENTIAL ADDRESS

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A SHORT two score years ago, a new department of medicine was born, like Venus, from the sea, conceived in Actinia and sired by a dog named Neptune. Delivered by a physiologist in Paris, it was wet-nursed by ten thousand guinea pigs. This was truly an incubator baby, spending its first few years exclusively in the laboratory. It was christened "Allergy."

Soon it became apparent that, although a changeling, this waif must be accorded a place with its brethren, in the family of diseases. Many looked upon it as an ugly duckling, while a few, attracted by its strangeness, gave it study and guidance.

As time went on, those who were interested in this lustily growing child found themselves drawn together by common interest. This society and others were organized for the collaborative study of phases of allergy.

In the seventeen years since our first meeting, the literature of allergy has increased to a surprising extent. The 1924 *Quarterly Cumulative Index* devoted 22 running inches to anaphylaxis and allergy. By 1939, this had grown to 114 inches. At least one article on allergy appears in nearly every issue of the general medical periodicals. A journal devoted exclusively to the subject has now reached its eleventh year. Texts and reference books are appearing, almost in bewildering profusion. The name has become a parlor password, a catchword, subject for humor, ribald and semiserious. It appears in the daily press, without explanation and on the assumption that all know its significance. Allergy has arrived!

Like most adolescents, it is gangling, clumsy, overenthusiastic, self-assured. In the exuberance of youth it has not yet found time to settle down to its proper place in the cosmogony of disease. It has now reached a turning point in its career. Will it, like its bumptious elder brother, Endocrinology, assume a sober, dignified, and withal helpful and important position in the society of diseases? We may well ask in this year, 1940, when our specialty is about to assume long trousers, What of the future of allergy?

There may be some who would question my assay of the past, who still believe that allergy is a flash in the pan, scheduled for ultimate oblivion. In medicine, there are ships that pass in the night. We recognize them in the fads and fancies, promulgated from time to time

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for the treatment of chronic diseases such as asthma, migraine, urticaria, and eczema. Now and again, new methods are proposed as "better than." They receive enthusiastic trial, the results of which may quite fill the literature of medicine. Then, like the ships, they are forgotten. But there are other ships, sometimes so far away that we can but distinguish their lights. We may not be able even to give them names. Possibly they remain for a long time on the horizon, and as we near port, they may loom closer. We watch them as, at last, they reach their destination of achievement.

In its infancy, clinical allergy was just such a ship. Any vessel which has held true to its course thirty-eight years after the laying of its keel in a Paris laboratory, and for thirty years since its launching into the sea of clinical medicine, sustains little likelihood of becoming lost or of foundering. During this same period many ships traveling the same lane have passed and have remained unreported. We might name a few of them: acidosis, iontophoresis, urinary proteose, calcium, potassium chloride, histaminase, and cortical hormone. Possibly some are just beyond the horizon and will show up later, as we near port. But our own ship has weathered the storm and has established its seaworthiness.

What of its future?

What I see in the crystal of the future may be altogether dissimilar to anything that you may see, but I present it to you as I see it. Time alone will determine its correctness.

The past history of allergy may be divided roughly into three epochs. The first is preclinical and may be spoken of as the period of *experimental anaphylaxis.* In it, research students were investigating a curious laboratory phenomenon, not suspecting possible relationship with any common human ailment, although their observations did appear to explain a very uncommon, man-made malady known as serum sickness.

We might term the second phase as that of *applied anaphylaxis,* in which laboratory investigators and clinicians recognized certain common clinical disorders as dependent upon a mechanism similar to that observed in experimental anaphylaxis. During this period the concept of protein poisoning or protein sensitization was dominant. Clinical investigators spoke and thought in terms of the protein antigen, either alone or combined with hapten.

The third stage was opened with the realization that nonprotein and nonhapten excitants might cause clinically allergic reactions, with symptoms indistinguishable from those due to protein sensitization. Thus were included contact allergy, sensitization even to pure chemical elements such as nickel, and an allergic type of reaction to physical factors such as heat, cold, and sunlight. Naturally this required a broadening of the concept and of the definitions of allergy. It is at this stage that we find ourselves today.

Explanatory theories have been developed which roughly parallel the broadening of our allergic concepts. The Ehrlich side-chain theory, which, for better or for worse, is still used, despite all of its defects, as the most graphically understandable explanation of protein sensitization, has had added to it the Lewis theory of the H-substance. We can now say glibly that living cells with sessile antibodies, injured by the attachment of alien antigen, release histamine or a histamine-like substance, which, in turn, produces those physiologic changes in the capillaries and smooth muscles and possibly elsewhere which are directly responsible for the symptoms of the allergic response. We can postulate that in physical allergy predisposed cells may be directly injured by the effect of heat or sunlight, so that they automatically release histamine without the intermediation of an allergenic excitant.

I have gone farther in my own efforts to rationalize allergy as a defect in the mechanism of protection.

Years ago it was thought that there were two possible explanations of antibody response. An abundance of free circulating antibodies created protection or immunity. In their absence, antibodies, attached to the cells, created a state of increased susceptibility. Desensitization might be accomplished (a) by exhaustion or saturation of sessile antibodies or (b) by stimulation of cellular activity, with consequent production of large quantities of free protective antibodies. Today I feel that we can dismiss the former.

That there are free antibodies in allergic persons is demonstrated by reagin transfer in the Prausnitz-Küstner reaction. The work of Cooke and his associates, confirmed by Langner and Kern and by Loveless, indicates that these free antibodies are increased after hyposensitization. It is true that those which appear after desensitization may be of slightly different character, but they appear to be equally specific antibodies and are probably identical or closely related.

Let us attempt to visualize allergy as a hereditary defect, possibly inherited as a partial recessive, in accordance with the theory of Weiner. We must then talk of defective genes and think in terms of diseases such as hemophilia, albinism, and similar inherited tendencies.

In the case of allergy, what is it that *might* be inherited? One thing that might be inherited, as I see it, is cellular maturation of antibodies. Normal cells produce antibodies which are first sessile or attached, and then are shed into the body fluids. In allergy, maturation stops before completion, at the stage of shedding. Some are shed, but not in normal abundance. Possibly those that are shed are of poor quality. This would explain Cooke's suggestion that reagins and the immune antibodies are not identical. This, then, becomes a developmental defect.

What happens during the process of hyposensitization? Repeated injections of the allergen stimulate the cells to greater activity, and, for a time, greater numbers of matured antibodies are produced and liberated. The normal process of protection has been completed. As

long as this artificial stimulation is continued, cells perform more efficiently. With discontinuance of hyposensitization, however, they gradually revert, and the inherited defect of uncompleted maturation again becomes evident as a defective reaction of protection.

To me this concept of a maturation defect constitutes almost the last link in rationalizing the allergic response. It enables us to explain the heredity factor, the chemistry of allergy, the relationship between allergy and immunity, and it is based upon and utilizes the two most popular concepts today, that of protective antibodies and the theory of the H-substance. It enables us to talk of immunization against allergens. I must confess to a preference for this term rather than desensitization. To me, immunization more nearly indicates what actually happens.

I do not wish to imply that I believe these theories to be the final explanation. Theories are but steppingstones in our progress. They are essential and are based upon the knowledge of the day. With increasing knowledge, they must be discarded. We will find more steppingstones along our route, until at last we reach the summit.

I should like to summarize in a single sentence past achievements in clinical allergy, in contradistinction to what I believe to be hidden in the future. Today we are treating only the episodes of allergy, not allergy itself. Our attention is riveted upon the excitants of allergy, upon the allergens. If we cannot arrange for the patient to avoid exposure to the allergenic excitants, we subject him to a period of hyposensitization against it. As Richet once said to me, "We pay much attention to the excitant, sometimes to the exclusion of the terrain in which it is exerting its activity."

We might speak of the present period in the evolution of allergy as that of *allergic specificity*. Realization of the specificity of the reaction is of utmost importance and future progress will depend upon the pioneer work that has been done, but I believe that the next, or fourth, step will involve increasing attention to the terrain, to the study of the altered physiology of the allergic response.

There is more to the allergic state than the development of sensitization. We must learn what physiologic difference there is between the nonallergic and the allergic person, which causes the latter to react as he does. We may infer from the studies made on the inheritance of allergy that heredity plays a part. But this is no explanation of the altered physiology of the response. It is merely an additional factor.

Around the middle of the last century, clinicians toyed with the word *diathesis*. They had little understanding of its significance. It was an inclusive term, indicating a tendency or predisposition. Today we might speak of the allergic diathesis or the allergic constitution. Behind closed doors, we might agree that we know very little about it. We are, however, on the threshold of a clearer understanding and I believe that before long we will know as much about the patient with

allergy as we do of his allergy itself. Recent developments in the study of the autonomic nervous system appear to have a definite bearing on our understanding of the allergic constitution.

The late Dr. T. Wingate Todd very aptly expressed the difference between study of the excitants and of the terrain, when he wrote: "The result of shaking a stick at a dog depends less on that gesture than on the condition of the animal at the moment. What is true of the dog is true of the human being. The impact of a stimulus may be far less significant than the condition of the organism which receives the stimulus. Certainly this is true in allergy. Hence, consideration of the constitution becomes of the greatest importance."

Lewis Webb Hill has likewise expressed his conviction that for the solution of the problems of allergy we must explore deeper than the level of response to antigens. He has written as follows: "At the present time we would probably all agree that the present method of attack, that is, removal of what seem to be significant allergens, as determined by skin hypersensitivity, the history, and possibly by elimination diets, is the best immunologic approach now available, and that there is considerable evidence to show that it is founded upon sound principles; furthermore, that it sometimes works.

"It does not, however, solve the problem. It is fairly good, but not good enough; one cannot be satisfied with it; it is not effective enough to make one feel that this is all there is to it, and that he has a really adequate therapy at hand, even when combined with all other possible measures. There is a large gap which must be filled if this disorder is ever to be understood, and I think that those of us who have been especially interested in it, although we do help a good many cases, become less and less satisfied with our therapy in proportion to the number of cases we have seen."

As I see it, the trend of the allergy of the future will be toward a broadened outlook, beyond specificity, and in the direction of more detailed study of its physiology. Until now, we have studied the chemistry of allergy and we have learned much. Now, we must learn how these chemical alterations affect the human organism.

We speak of asthma. Is there just one asthma, or are we including two or more separate diseases under one generic name, as was done for so long with eczema? This same question applies to other allergic manifestations.

Allergy appears to be increasing with the increasing artificiality of our environment. Will we eventually find that some cellular deficiency resulting from as yet undetermined dietary deficiencies is playing a part? There is evidence suggesting this as a possibility.

We are accustomed to speak of allergy as a struggling new branch of medicine. This is no longer the case. As Dr. Harry Alexander remarked to me recently, "Clinical allergy has already matured. It

has reached that stage at which atopic disorders and contact dermatitis are now as clearly understood as they are likely to be for some years to come. Their clinical aspects have been pretty well worked over. Further progress must depend upon the development of new concepts or the making of new discoveries." Just as I see the Allergic Constitution looming large in the crystal of the future, Alexander sees the possibilities of great progress in the field of Bacterial Allergy. Both fields and many others will be explored, and I venture to say that we will find that the several paths will converge. Each path is indeed but a byroad which parallels, more or less, the main trail of Internal Medicine.

There is a long rangy mountain south of Geneva called the Grand Salève. In those days when mountain climbing was a pastime for your present speaker, I started with two companions to climb the Salève. Since our climbing abilities and speeds differed, we agreed to meet at the top and selected different routes. I took what I believed was the straighter though more difficult climb. Let us call it the path of Allergy. The friend on my right chose a trail I shall label "Dermatology." The one on the left went by "Gastroenterology." There were other paths. We all had the same objective—the mountain top from which the view would be clear and unobstructed.

After I had passed the first small peak, I came to an upland valley where some shepherds lived, tending their flocks. They shouted to me that I was on the wrong path, but I saw what I believed to be the summit, straight ahead, and continued onward. As the road grew steeper, I traversed some heavy shale, nearly losing my footing. With constant effort, however, I at last reached the peak, only to discover that there was another one, still higher and farther on. As I traversed the saddle, edging a bit to the right, two barking dogs nearly persuaded me to cease my efforts.

Stimulated by the realization that my friends were undergoing similar experiences, I continued my struggle. At last I scaled the highest peak. The sun was in the west and the view was magnificent. Quite a distance down on the right I saw one of my comrades, struggling up his path, and knew that before long he too would be standing beside me, enjoying the panorama of the future. Looking down to the left I realized that the path of Gastroenterology and several others would eventually lead to our vantage point.

From where I stood, a broader path led on to the west, gradually dropping toward the valley of the Rhone. It was a path on which three or more could travel abreast.

As I looked into the valley, I saw Geneva in the distance, from whence we had started. I also saw a much wider path, indeed a broad motor highway, which merely skirted the mountain, continuing onward toward the setting sun. It was the highway of Internal Medicine.

When my friends had caught up with me, we started down the pleasant western slope. As we walked along, we compared experiences. Although we had been on the same mountain, our views had all been different.

Another climber caught up with us. He had followed the path of Rhinology. He, like ourselves, had enjoyed the climb. As we drew nearer to the highway, we regretted leaving the mountain. It had been such fun traversing paths explored by but a few. We had seen perspectives. We had viewed panoramas which had been denied to those who had remained in the fog-filled valley. When at last we reached the road, our friends who had come along the highway met us with their car.

We joined them and rode on into the night, happy in the knowledge that the sun would soon rise again over the Grand Salève, that mountain the scaling of which had given us a degree of pleasure which was incomprehensible to those who had chosen to remain in the lowlands.

POISON OAK AND POISON IVY*

1. Dermatitant Units as a Standard Measure of Potency for Extracts From These Plants

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IN 1923, McNair[1] proved conclusively that the constituent in the poison oak plant *(Rhus diversiloba)* which causes dermatitis is a clear, amber-red, oily, nonvolatile, viscous, poisonous liquid, the chemical behavior of which is that of a polyhydriephenol. To this he gave the name lobinol and outlined in detail a method for its separation. From *Rhus vernicifera,* the plant of which Japanese lacquer is made, Majima,[2] in 1922, isolated a substance similar to lobinol in its chemical composition as well as in its injurious effects on human beings, and this he called urushiol. Later (1934) Hill and his co-workers[3] discovered that toxicodendrol, the active agent in poison ivy *(Rhus toxicodendron),* was identical with that in the Japanese plant.

In addition to these nonvolatile oils, both poison oak and poison ivy contain glucosides, enzymes, and other constituents, the exact nature and properties of which have not as yet been evaluated.

Granting the current assumption that lobinol and toxicodendrol, when brought in contact with susceptible skins, are the only substances in poison oak and poison ivy responsible for the erythema and vesiculation, there is on record no scientific proof that this fraction from these plants, when administered internally, by mouth or by injection, has any antigenic or desensitizing properties. Thus, it seems that until it is scientifically established which fraction, if any, is responsible for inhibiting such sensitization, all preparations of poison oak and poison ivy, when intended for use in the prevention or treatment of the dermatitis resulting from contact with these plants, should contain all of the plant constituents.

As a preliminary experiment, I prepared several extracts of both poison oak and poison ivy, macerating over a period of several weeks the leaves and stems (in quantities of about 10 per cent) in various solvents, i.e., petroleum ether, alcohol, acetone, etc. After filtering, the solutions were concentrated by distillation under vacuum at a temperature not above 60° C. In order to weigh the solids, portions of these concentrates were further evaporated to dryness. I then prepared accurate dilutions, beginning with dilutions of 1:10.

These extracts, in similar strength dilutions, that is, each containing the same ratio of solids content, were tested on the skins of the same

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laboratory animals for their ability to produce dermatitis. A great variability was demonstrated, some extracts being much more potent than others. Many factors undoubtedly play a part in this variability. For instance, several investigators have reported differences in the virulence of the poison in plants gathered at one season of the year as compared to those gathered at another. Interestingly enough, I found that, weight for weight, the solid extracts obtained from the dried leaves and stems were more potent in this regard than those made from the fresh plant. This might explain, in part at least, why the various poison oak and poison ivy preparations being offered to the medical profession today as therapeutic agents vary so much in their action, there being no "United States Potency Standard." In the first place, most of them are prepared on the basis of solids content only; and in the second place, there is no uniformity of dilution. One manufacturer's product will contain one part solids in 160; another's, one part in 10,000. This same fluctuation in the potency of the basic extracts could explain, too, the lack of uniformity in the results obtained with skin tests by different investigators.

In the light of our recent knowledge, the lobinol and toxicodendrol contents in preparations of poison oak and poison ivy can be measured accurately now on the basis of their dermatitis-producing activity, and I suggest, therefore, that, as a standard, units which I shall describe as "dermatitant" be adopted as a measure of potency. (McNair[1] uses the term "dermatitant" to describe the action of lobinol on the skin, and I interpret it to mean a substance having the property of producing a vesicular dermatitis when brought in contact with susceptible skin.)

On this basis, I have selected as representing 10,000 dermatitant units that quantity of poison oak or poison ivy extract contained in 0.1 c.c. of designated solvents, which, when applied "without cover" to the epilated skin of animals which do not become sensitized, such as the rabbit, rat, or mouse, in the form of a stripe (3 cm. in length by 6 mm. in width) is just sufficient to elicit an erythematous reaction within forty-eight hours.

The designated solvents mentioned above are petroleum ether, alcohol, or acetone. When sensitized guinea pig skins are tested with extracts dissolved in one of these three, reactions occur with much higher dilutions than with those dissolved in nonvolatile solvents such as the oils glycols. After the dermatitant activity of an extract is determined in these solvents, it can then be incorporated in a vehicle more suitable for internal administration by driving off the volatile solvent either before or after mixing with one which is nonvolatile.

The skins of white female animals were finally adopted as a standard. The hair of these animals was removed in three different ways: by plucking; by clipping and then shaving; and by clipping followed

by the application of a depilatory. After epilating, twenty-four hours were allowed to elapse before the testing was done, and the final results were the same regardless of the epilation technique used.

When poison oak or poison ivy extracts were applied to the skins of rabbits, rats, and mice, a reaction similar to that observed following the application of a primary irritant resulted. That is, when these extracts contain concentrates of lobinol or toxicodendrol above a certain level, they produce an erythematous skin reaction, the degree of which is constant for the given strength; when concentrates below this level are applied, no reaction occurs.

It was found that an epilated skin area in the rabbit, rat, and mouse gave an erythematous response to the stripe application of 0.1 c.c. containing 10,000 dermatitant units. One-tenth cubic centimeter containing less than this amount constantly failed to elicit a response, while 0.1 c.c. applications containing more than this amount always resulted in a more intense reaction. The type of reaction was a red edematous line, appearing within twenty-four hours and becoming more intense during the next twenty-four hours. This reaction lasted about four days, becoming crusted and the crust separating on about the eighth day. I was not able with these three animals to render their skins more sensitive or less sensitive by multiple paintings (Table I and Fig. 1). For this reason, the skin of one or all of these three animals (personally I prefer the rabbit) offers an excellent medium for determining the lobinol or toxicodendrol content of these extracts.

TABLE I

MULTIPLE SKIN TESTS WITH VARIOUS STRENGTH SOLUTIONS OF POISON OAK AND POISON IVY WHICH FAILED TO SENSITIZE THE NUMEROUS RABBITS, RATS, AND MICE SO TESTED

D. U.*	9/21	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30	10/11	10/20	12/19
100,000	+	+	+	+	+	+	+	+	+	+	+	+	+
10,000	+	+	+	+	+	+	+	+	+	+	+	+	+
1,000	–	–	–	–	–	–	–	–	–	–	–	–	–
200	–	–	–	–	–	–	–	–	–	–	–	–	–
100	–	–	–	–	–	–	–	–	–	–	–	–	–

*D. U.=Dermatitant units in 0.1 c.c.

After 10,000 dermatitant units have been measured in this manner, the preparation can then be diluted or concentrated in order to have 0.1 c.c. represent one unit, 100,000 units, or any number of units between these two extremes.

Following the initial application of the various dilutions, the guinea pig reacts in the same manner as do the other three animals; that is, concentrates above the same level as those used on the rabbits, rats, and mice cause a similar reaction, while those below that level are negative. From this point on, however, the behavior of the guinea pig's skin is entirely different. In contrast to the skins of other animals, the guinea

pig's skin becomes sensitized, and thereafter for a certain period of time, the duration of which has not yet been determined, the skin will react to applications of much weaker solutions.

TABLE II

MULTIPLE SKIN TESTS MADE ON NUMEROUS NONSENSITIZED GUINEA PIGS WITH VARIOUS STRENGTH SOLUTIONS OF POISON OAK AND POISON IVY*

D. U.†	9/21	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30	10/11	10/20	12/19
100,000	+	+	+	+	+	+	+	+	+	+	+	+	+
10,000	+	+	+	+	+	+	+	+	+	+	+	+	+
1,000	-	-	+	+	+	+	+	+	+	+	+	+	+
200	-	-	-	-	-	+	+	+	+	+	+	+	+
100	-	-	-	-	-	-	-	-	-	-	-	-	-

*The animals became sensitive to 1/10 of the minimum initial reactive dose on the third day and to 1/50 on the sixth day.

†D. U.=Dermatitant units in 0.1 c.c.

After several daily applications (Table II and Fig. 2) an erythematous vesicular response could be elicited with 0.1 c.c. containing 1,000 dermatitant units, with 0.1 c.c. containing 200 dermatitant units, and occasionally with 0.1 c.c. containing only 100 dermatitant units.

Simon, Simon, Rackemann, and Dienes[4] were the first to report on the susceptibility of the guinea pig's skin to poison ivy. They found that this animal could be sensitized only by painting its skin with the extracts. They were unsuccessful, as I was with all four animals, in sensitizing or desensitizing guinea pigs by intradermal, subcutaneous, or intramuscular injections of the extracts.

Cross testing with poison ivy extracts the skin of guinea pigs sensitized to poison oak extracts, and vice versa, gave positive results, indicating that lobinol and toxicodendrol are as similar in their biologic action as they are chemically. For confirmation it only remains to be shown that desensitization of the skin with one chemical will afford protection against the other. Biederman[5] recently reported clinical tests which seemed to indicate that such desensitization is possible.

The concentrates from which the first standards were prepared contained 13 per cent solids in acetone and were very potent in their dermatitant activity.* After some experimenting, I discovered that these particular specimens, when further diluted with acetone until their solids content represented 10 per cent instead of 13, had the following dermatitant unit values:

0.1 c.c. containing 0.01 gm. of solids = 100,000 dermatitant units
0.1 c.c. containing 0.001 gm. of solids = 10,000 dermatitant units
0.1 c.c. containing 0.0001 gm. of solids = 1,000 dermatitant units
0.1 c.c. containing 0.00002 gm. of solids = 200 dermatitant units
0.1 c.c. containing 0.00001 gm. of solids = 100 dermatitant units

In these particular specimens, the solids content paralleled the dermatitant unit content. That this is not always the case was soon

*Dr. S. D. Beard, director of the Lederle Laboratories, was kind enough to furnish me with their concentrates of both poison oak and poison ivy.

discovered by testing the products of other laboratories as well as those which I prepared myself. Actually, if preparations of poison oak or poison ivy are to be standardized on the basis of their dermatitant activity, there is no necessity for knowing or even ascertaining their solids content.

The correlation between the behavior of these poison oak and poison ivy extracts so standardized on animal skins and their behavior on human skins was made on the basis of the results observed with numerous animals of the various species and with thirty adult volunteers.

Fig. 1.

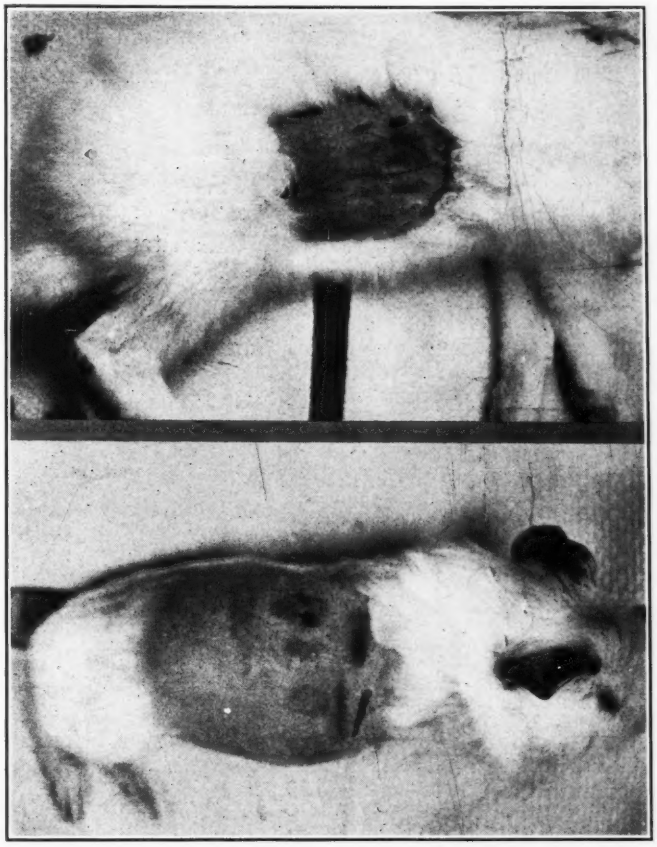

Fig. 2.

Fig. 1.—Rabbit No. 1251, stripe tested daily with four different strength solutions of 0.1 c.c., each of which contained, respectively, 100,000, 10,000, 1,000, and 200 dermatitant units. An erythematous reaction occurred daily from the applications of the two stronger solutions. The weaker solutions caused no reaction. See Table I.

Fig. 2.—A nonsensitized guinea pig stripe tested daily with four different strength solutions of 0.1 c.c., each of which contained, respectively, 100,000, 10,000, 1,000, and 200 dermatitant units. An erythematous reaction occurred daily from the applications of the two stronger solutions. The third dilution, containing 1,000 D. U., became positive on the fourth day, indicating sensitization. See Table II.

The same technique of applying the tests was utilized for human skin as for that of animals; that is, 0.1 c.c. of the various strength extracts in either petroleum ether, acetone, or alcohol solvents was applied to the flexor surface of the forearm in the form of a stripe

3 cm. in length by 6 mm. in width and by means of a small cotton swab. (This dries rapidly.) The test area was not covered, and the patient was instructed not to wash the arm during the ensuing twenty-four hours.

According to the reactions which followed the applications of these extracts, the thirty subjects were divided into three groups.

Group 1 was made up of those who were already sensitized. Sixteen, or 53.3 per cent, comprised this group. All gave a history of one or more outbreaks of poison oak or poison ivy dermatitis. Within twenty-four, forty-eight, or seventy-two hours following the application of 0.1 c.c. containing 1,000 or more dermatitant units, there appeared erythematous skin reactions of varying degrees of severity, depending upon the strength of the application.

When applied in this manner, 1,000 dermatitant units proved to be the smallest amount of extract capable of eliciting an erythematous response in these sensitized individuals. The erythematous stripe resulting from the application of 1,000 dermatitant units caused no subjective symptoms, nor was there any spread of the dermatitis in the subjects tested with this amount.

When 0.1 c.c. quantities, each containing respectively 500, 250, and 100 dermatitant units, were applied in this manner to the skins of these sensitized individuals, no reaction occurred; but 0.1 c.c. applications, each containing, respectively, 2,500, 5,000, 10,000, and 100,000 dermatitant units, elicited definite erythematous responses, sometimes within twenty-four hours. In the case of the stronger applications, there also occurred some weeping, extension of the dermatitis, and discomfort. This observation was interesting in view of the fact that, despite the wide variations which are known to exist in human susceptibility to these plants, the threshold of reaction for this entire group was so uniform that I am of the opinion that, with this technique, sensitized human skins could be used as an additional medium with which to standardize these extracts. However, when tests were made on this group with the "under cover" method, 1,000 dermatitant units caused many different degrees of erythematous reactions ranging from one-plus in mildly susceptible persons to four-plus in extremely susceptible ones. On further experimenting, it was also found that some members of this group would give an erythematous reaction to as little as 10 dermatitant units when the "under cover" method was used.

Group 2 consisted of those who were not as yet sensitized, but whose skins were, nevertheless, susceptible. Six, or 20 per cent, made up this group. None of them gave a history of ever having had poison oak or poison ivy dermatitis, although most of them thought that they had been exposed on several occasions.

The skin reactions in this group were very interesting. In contra-

distinction to those persons already sensitized and whose skins reacted within twenty-four to seventy-two hours to the testing, nothing happened in this group until the seventh day following the simultaneous applications of 0.1 c.c., each containing, respectively, 100,000, 10,000, 1,000, and 500 dermatitant units. On the seventh day an erythematous linear reaction appeared at the site of the 100,000 unit stripe only. There were no subjective symptoms at that time, but from the twelfth to fourteenth days a dermatitis began to appear about this area. The second stripe site (10,000 units) then became positive; the dermatitis spread, the whole arm became edematous, and the patients were in considerable distress for the ensuing three to four weeks. Several weeks after all reactions had subsided, the minimum reactive dose in these persons whom I had sensitized was determined by retesting with small doses. It was found to be the same for this group as for those placed in Group 1 (those already sensitized when first tested), that is, 0.1 c.c. containing 1,000 units when applied "without cover" (Fig. 3).

Fig. 3.—An already sensitized skin stripe tested with 1,000, 500, and 100 dermatitant units, showing on the third day an erythematous reaction to the 1,000 D. U. application only.

In Group 3 were those whose skin tests were negative. Eight, or 26.7 per cent, made up this group. Some gave a history of having had severe outbreaks of poison oak or poison ivy dermatitis when children; others had no knowledge of ever having been affected. Following the simultaneous applications of 0.1 c.c., each containing, respectively, 100,000, 10,000, 1,000, and 500 dermatitant units, no reaction of any kind occurred. Four of these subjects allowed me to retest their skins several times, using stronger extracts, and each time results were negative.

COMMENT

For the purpose of this study, I chose the "without cover" method of testing. It seemed advisable for three reasons: first, because the stripe testing "without cover" more closely simulates the manner in which skin contact is made with plants in nature; second, because the re-

sults obtained with 1,000 dermatitant units in sensitized human skins so tested were uniform, while the results obtained from tests made "under cover," though more sensitive, were not uniform; third, because it is practically impossible to keep a cover over such areas on an animal's skin, and the preliminary testing of extracts to determine their dermatitant strength must be done on animals. Therefore, by using the same technique in human skins it was much easier to correlate and compare results obtained in the two groups.

The fact that the nonsensitized human skins tested did not react within twenty-four hours to extracts of poison oak and poison ivy in however concentrated a form they were applied is against the assumption that we are dealing here with primary irritants per se; yet the behavior of these extracts on the skins of the three types of animals which do not become sensitized, namely, the rabbit, rat, and mouse, is strongly in favor of such an interpretation, at least in so far as the epilated skins of animals are concerned. The guinea pig reacts in a similar manner to the initial application of these concentrates, but it would seem that the dermal cells of the guinea pig and the human can develop an antibody-like substance which is responsible for their sensitization.

Antibodies have not as yet been demonstrated in the blood serum of animals or humans whose skins are sensitized to these plants. However, precipitins, reagins, and anaphylactic reactions are now being sought for.

The adoption of the dermatitant unit as a standard measure of potency might be a step in the right direction, although, of course, a "neutralizing unit" would be worth a great deal more to physicians who are called upon to alleviate the symptoms of their patients.

The establishment of any type of unit must necessarily be arbitrary. However, after it was found that the solids content in extracts of poison oak and poison ivy was not an accurate gauge of their potency, and after it was further shown that the percentage of lobinol and toxicodendrol contained in any of these concentrated extracts could be reliably determined by applying a measured amount of the extract to the skins of animals incapable of being sensitized, it seemed at least that a preliminary titration standard was available.

Allergists attempting to desensitize patients suffering from other allergies begin by using extracts containing a fraction of the minimum reactive dose and increase it gradually. So, in the case of poison oak and poison ivy desensitization, if there is any rationale for this type of therapy at all, I should think small doses rather than the large doses contained in certain manufacturer's products would be preferable. I would, therefore, like to recommend that, for the present, extracts be dispensed in two rubber-capped vials, one to contain 100 dermatitant units per 0.1 c.c., the other to contain 1,000 units per 0.1 c.c. The

clinician could then begin by injecting 0.1 c.c. of the weaker dilution, increasing the amount by 0.1 c.c. at each injection until a dose of 1,000 units or 1 c.c. of this strength is given. He could then continue with the stronger extract, beginning with 0.1 c.c. containing 1,000 units and increasing it as indicated. A skin test could be made with either of these solutions, the stronger to be used first "without cover" as a qualitative test, the weaker to be used later "under cover" to determine the degree of sensitiveness. In the meantime, the results should be recorded in the manner recommended by Caulfeild.[6]

SUMMARY

Extracts of poison oak and poison ivy were tested on animal and human skins. In view of the definite information obtained from these tests, the dermatitant unit is suggested as a standard measure of potency.

Methods are described for measuring an exact number of units by first titrating the extracts on animal skin. The behavior of a given number of units on sensitized and susceptible subjects is also discussed.

The dispensing of these extracts so that skin tests and graduated doses can be conveniently administered is recommended.

I wish to acknowledge my gratitude to Dr. S. D. Beard, Director of the Lederle Laboratories, to Dr. John Reichel, Director of the Sharpe and Dohme Laboratories, and to Dr. Harry E. Foster, Director of the Cutter Laboratories, for having furnished me with concentrates of poison oak and/or poison ivy extracts; to Parke, Davis and Company for furnishing me with their fluidextract of *Rhus toxicodendron* as well as several pounds of dried leaves of poison ivy; and to Mr. H. H. Fehr of the Mulford Colloid Laboratories for having gathered and shipped to me fresh ivy leaves.

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SUSCEPTIBILITY TO POISON IVY DERMATITIS

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THE dermatitis produced by contact with the poison ivy plant is extremely common. It is usually estimated that about 60 per cent of the general population is clinically susceptible to this distressing skin disease. Patch tests with plant extracts have shown a higher percentage.[1] In these determinations, the plant oleoresin which is used in the test and is responsible for the dermatitis is placed on the skin in an excessive concentration seldom duplicated in nature. Spain, Newell, and Meeker[2] have shown that the percentage of susceptibles increases with the concentration of the test material and varies as the logarithm of the concentration of irritant applied.

Although some attempts have been made in the literature to correlate variations in clinical susceptibility to the poison ivy dermatitis and individual physical characteristics, this phase of the subject has not received much attention other than speculation. Lindley[3] thought that blondes were more susceptible, an opinion shared by Ward.[4] Baldwin[5] stated that obese people were most susceptible. Horsfield[6] and Dakin[7] believed that children were more susceptible than adults. McNair[8] felt that age may influence immunity, but there was no proof that children as a class are more susceptible than adults. Coca[9] performed patch tests on twelve adults over 20 years of age and also on twelve children all 5 years old or younger. He concluded that the age incidence of dermatitis venenata increases greatly from childhood to adult life and reaches a high percentage, probably about 90 per cent.

Krause and Weidman[10] studied twenty patients by patch test and clinical history. They concluded that there was no difference in susceptibility between blondes and brunettes or between obese and thin patients. The histories showed a peak of susceptibility between the ages of 14 and 16 years.

Frequent attempts have been made to classify the dermatitis of poison ivy in the same category as that of hay fever and similar allergic phenomena. Knowles, Decker, Pratt, and Clarke[11] studied several hundred medical students with patch tests for poison ivy susceptibility. They found that 36.5 per cent of the persons with positive patch tests also had a positive history for the common forms of allergy. The same positive history was also obtained in 36.0 per cent of the persons with negative patch tests. They concluded that there was no significant correlation between susceptibility to poison ivy as shown by a positive patch test and a history of the more common forms of allergy.

During the summer of 1938, an opportunity presented itself to secure clinical information of poison ivy incidence in a large series of cases at

Treasure Island, N. J., a summer camp maintained by the Philadelphia Boy Scout Council for boy scouts and their adult leaders. The peculiar advantages of this camp for accurate work in poison ivy have been described in a previous paper.[12]

Treasure Island Camp is located on a small island where the poison ivy plant grows luxuriantly. Campers are confined to the island for virtually their entire stay of one or two weeks. This insures for all a uniform and intimate contact with the poison ivy plant.

An individual clinical record was made of all campers, and the resultant data were analyzed. There were 1,925 records, some of them incomplete for various reasons. In the succeeding analyses, records that were lacking in pertinent information were omitted from consideration in each instance.

Records were first divided on the basis of age, and determinations were made of the percentage of poison ivy dermatitis acquired in each age group. Calculations were based on susceptible individuals only. Susceptibility, in turn, was based exclusively on a history of poison ivy dermatitis in the past or during this investigation. The results are presented in Table I. Since all campers had a uniform opportunity to

TABLE I

RELATION OF POISON IVY SUSCEPTIBILITY TO AGE

AGE	TOTAL RECORDS	KNOWN SUSCEPTIBLES	POISON IVY DURING STUDY	PERCENTAGE
12	283	146	78	53.4
13	442	194	95	49.0
14	409	237	121	51.1
15	283	162	78	48.1
16	174	104	59	56.7
17	76	44	16	36.4
18	58	33	13	39.4
19	32	21	8	38.1
20-29	89	41	9	22.0
30 or over	33	11	3	27.3
Total	1,879	993	480	48.3

acquire poison ivy dermatitis, it was assumed that the incidence of acquisition during the study period was a comparative index of the degree of susceptibility at the time. Using this criterion, there is noted a definite and marked loss of sensitivity with increase in age.

Individual records were then compared with the Baldwin Tables of Average Age, Height, and Weight for Males in the Eastern United States.[13] It was arbitrarily decided to consider more than 10 per cent above average weight as an indication of obesity and more than 10 per cent below average weight as underweight. The records were then tabulated as described above, and the results of this compilation are recorded in Table II. There is noted a marked constancy of susceptibility irrespective of weight.

TABLE II

RELATION OF POISON IVY SUSCEPTIBILITY TO WEIGHT

WEIGHT	TOTAL RECORDS	KNOWN SUSCEPTIBLES	POISON IVY DURING STUDY	PERCENTAGE
Average	1,038	557	279	50.1
Obese	275	146	71	48.6
Underweight	210	111	55	49.6
Unknown	234	127	63	49.6

TABLE III

RELATION OF POISON IVY SUSCEPTIBILITY TO COMPLEXION

HAIR COLOR	TOTAL RECORDS	KNOWN SUSCEPTIBLES	POISON IVY DURING STUDY	PERCENTAGE
Light (red and blonde)	382	237	123	51.9
Medium (light and medium brown)	955	544	281	51.7
Dark (dark brown and black)	575	319	169	52.7

Correlation of susceptibility to hair color was next studied. Table III shows the resultant tabulation, and, again, no difference in susceptibility can be seen. A similar study was made comparing skin sensitivity to sunlight with susceptibility to poison ivy. The results, presented in Table IV, are equally negative.

TABLE IV

RELATION OF POISON IVY SUSCEPTIBILITY TO SENSITIVITY TO SUNLIGHT

DEGREE OF SKIN SENSITIVITY TO SUNLIGHT	TOTAL RECORDS	KNOWN SUSCEPTIBLES	POISON IVY DURING STUDY	PERCENTAGE
Blister easily	239	130	69	53.1
Tan slowly	1,008	577	287	49.8
Tan easily	654	392	221	56.4

TABLE V

RELATION OF POISON IVY SUSCEPTIBILITY TO EXPRESSIONS OF ATOPY

	TOTAL RECORDS	KNOWN SUSCEPTIBLES	POISON IVY DURING STUDY	PERCENTAGE
Hay Fever	142	89	49	55.1
Hives	170	106	58	54.8
Asthma and/or eczema	36	21	12	57.1
Total atopic	348	216	119	55.1
Nonatopic	1,577	896	461	51.5

The question of atopy was next investigated. All records were divided into those giving a positive and those giving a negative history for each of the common forms of atopy. Where the individual gave a history of allergic sensitivity for more than one form, the record was classified

under only one heading, preference being given in the following order: hay fever, asthma, eczema, hives. The results, presented in Table V, show virtually no relationship between common allergic sensitivity and poison ivy sensitivity.

CONCLUSIONS

The degree of susceptibility to poison ivy dermatitis is very great in boys from 12 to 16 years of age, but diminishes rapidly thereafter in older males.

There is no correlation between sensitivity to poison ivy and such physical characteristics as weight or hair color.

There is no correlation between sensitivity to sunlight and susceptibility to poison ivy.

There is no correlation between susceptibility to poison ivy and the commoner forms of allergy, such as hay fever, asthma, eczema, or hives.

The author wishes to acknowledge his indebtedness to the Philadelphia Boy Scout Council and especially to Mr. George Keller, director of Treasure Island Camp, for invaluable assistance in collecting the clinical records used in this paper.

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5254 OXFORD AVENUE

Special Reports

BRONCHIAL ASTHMA IN THREE PAIRS OF IDENTICAL TWINS

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THE purpose of this report is to describe briefly certain features in the bronchial asthma of three pairs of identical twins, and especially to show and discuss an interesting contrast in the pollen skin tests between the individuals in two of the pairs.

We have found statements about thirteen other pairs of twins, twelve definitely identical and one presumably so.[1-3] Seven pairs showed asthma in one individual only, and six pairs showed asthma in both individuals. Of the six pairs with asthma in both individuals, the sensitizations were said to be similar in three pairs, different in one pair, and were not mentioned in two pairs.

SKIN TESTS

On our patients some of the skin tests were done once, some twice, and some three times; in each case we recorded the strongest positive reaction. The only important differences between successive tests were in the third pair, and these differences were due to a generalized eczema, which made most of the skin unsuitable for testing. With the first two pairs that did not have eczema, tests were always done on both members on the same day, on the same sites and with the same materials.

CASE REPORTS

PAIR 1. *Clinical History.*—Dan and Dick were born July 7, 1934. The father had hay fever, and the mother's relatives had both hay fever and asthma.

Dan

1. Dan had no definite eczema.

2. The first attack of asthma occurred Oct. 24, 1937. There was some asthma nearly every day, varying from very slight wheezing and coughing to severe asthma, and becoming definitely worse during the ragweed season. In general, he was much better after very thorough house dust precautions and after treatment, mostly with stock vaccine and later with ragweed extract.

Dick

1. Dick had a mild facial eczema in infancy.

2. The first attack of asthma occurred in May, 1937. Dick was worse than Dan. He had some wheezing and coughing nearly every day, with many severe attacks, and he was worse during the ragweed season. In general, he was much better after very thorough house dust precautions and treatment with ragweed extract.

The ragweed tests were interesting in that, although Dan seemed clinically sensitive to ragweed, no positive skin test could be obtained by the scratch or intracutaneous method. He did, however, show a swelling and redness 2 inches in diameter after subcutaneous injection of 2,000 units of ragweed pollen extract. We believe, therefore, that he was clinically sensitive to ragweed, although in a lesser degree than Dick.

SKIN TESTS

	DAN	DICK
Rabbit	++	++
Feathers	+++	++
Orris	0	+
Dust	++	++
Timothy	0	+
Ragweed	0	+++
Wheat	+	+
Egg	0	+
Aspergillus	0	+
Oak	0	+

PAIR 2. *Clinical History.*—Charles and Henry were born April 23, 1922. The maternal grandmother had hay fever, but there was no known allergy in the father's family.

Charles

1. Charles had eczema.

2. Asthma occurred in July, 1935, and July, 1936. The second attack lasted a week and was moderately severe. There has been no definite asthma since, but he has noticed discomfort when sitting on a divan in the living room.

Henry

1. Henry had what may have been a mild facial eczema in infancy.

2. Asthma occurred in June, 1933, and in May, June, October, and December, 1935. He has had no definite asthma since, but has also noticed discomfort when sitting on the divan in the living room. In 1936 he had acute hemorrhagic nephritis and was at home when Charles had his attack of asthma at camp in July.

Neither boy had any important treatment.

SKIN TESTS

	CHARLES	HENRY
Feathers	+	++
Dust	+	+
Timothy	++	0
June grass	++	0
Orchard grass	++	0

The tests to the grasses are interesting in that, although Henry gave negative tests, three of his five attacks were in May and June. It seems probable to us that, despite negative tests, he, as well as Charles, had some clinical sensitivity to grasses.

It should also be noted that on July 1, 1936, Charles went to camp in New Hampshire while Henry stayed at home in Providence. At camp Charles had a moderate attack of asthma lasting about a week. Henry, at home, had no asthma that spring or summer. Charles reacted to skin tests with grasses, but Henry did not, after this incident. It seems not improbable that this difference in environment was responsible for the discrepancy.

PAIR 3. *Clinical History.*—Elizabeth and Ann were born in November, 1937. Their maternal grandfather had asthma, a maternal aunt had eczema, and the mother had urticaria during the nursing period.

Elizabeth

1. A generalized eczema began at 3 months of age after weaning and start-

Ann

1. A generalized eczema began at 3 months. It was more severe than that

ing a milk formula. She improved on evaporated milk and was still better on goat's milk.

2. The first attack of asthma was in May, 1939, and the second in September. Frequent severe attacks occurred from September through December, with wheezing much of the time in between.

of the twin, but otherwise had a similar course and still persists to a slight degree.

2. The first two attacks occurred at the same time as those of her twin. From September through December she has had six moderate attacks, but has been well in between.

Both children were much better after two months' treatment with house dust precautions and the weekly injection of house dust extract and stock mixed vaccine.

SKIN TESTS

	ELIZABETH	ANN
Kapok	+−	+
House dust	+	++
Timothy	+	++
Ragweed (short)	+	+−
Milk	++	++
Egg	+	+++
Silk	+	0
Cottonseed	+++	++
Giant ragweed	+	+−

DISCUSSION

In all three pairs, the age of onset, the severity of the asthma, and the allergen to which the patients were sensitive are very similar in the members of each pair. In the first pair, we believe that the difference in the skin tests for ragweed does not indicate an absolute difference in clinical sensitivity, but only one of degree. In the second pair, despite the difference in the skin tests with grass pollen extracts, probably both boys were clinically sensitive to grasses, although here also the degree of sensitivity may have been different. This difference may easily have been due to the difference in environment in July, 1936. Except those just mentioned, there were no important differences in either the histories or the skin tests between the individual members of each pair.

From our cases and the cases previously reported, it does not seem possible to draw any definite conclusions as to the influence of heredity upon the form of allergy or the specific sensitization developed. Since identical twins usually have, during infancy and childhood, practically identical environments, the frequency of similarity in form of allergy and in sensitizations does not necessarily imply that these are due to heredity. On the other hand, differences in these characteristics are common enough to suggest strongly that inheritance plays little or no part in determining the form of allergic response or the specific sensitization in allergic patients.

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PEPSIN ALLERGY

Case Report

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THERE is no record in the literature of pepsin acting as an allergenic substance, but the following case report illustrates that it may act as one.

CASE REPORT

In 1925, M. M., aged 16 years, was seen because of hay fever which manifested itself for the first time in 1924. He had rhinorrhea, sneezing, and itching of the eyes from mid-August to October 1. The family history indicated that one brother had hay fever, and another brother, urticaria solaris. The past history was essentially negative.

Physical examination was essentially negative except for a moderate obesity. The blood showed an eosinophilia of 5 per cent. Skin tests indicated a three-plus reaction to a 0.001 mixed ragweed extract. He received routine preseasonal treatment for a number of years, and lately he has received ragweed injections perennially. Preseasonal treatment resulted in about a 50 per cent improvement, while perennial treatment had improved his symptoms as much as 90 per cent.

In 1930, he became a pharmacist and has practiced his profession continuously. In 1935 he noticed occasional sneezing spells and rhinorrhea, but only while in the pharmacy. He paid very little attention to these spells at first, but inasmuch as they became more marked, he was advised to keep a daily record of attacks and note their time relationship to different drugs to which he was exposed in the course of the day. Repeated observations finally led to the incrimination of pepsin, caroid, pancreatin, and bile salts as the direct causes of the paroxysmal sneezing and rhinorrhea.

Pepsin, however, caused not only paroxysmal rhinorrhea and sneezing, but also asthma. Within half a minute after weighing any commercial powdered pepsin preparation, or even during the time of weighing, he invariably was seized with an itching of the nose and throat, followed by a spell of violent sneezing. If contact with pepsin was prolonged, an asthmatic paroxysm ensued which lasted well over an hour.

Extracts of pepsin, caroid, pancreatin, bile salts, and dust were prepared in buffered saline. After dilutions had been made and proved to be nonirritating on a large group of controls, the patient was tested intradermally. The results of these tests were as follows:

Pepsin, 1:100	+
Pancreatin, 1:10	++
Bile salts, 1:10	+
Caroid, 1:100	++
Dust, 1:10	+

To investigate the presence of reagins, passive transfer experiments were made with the patient's serum. These disclosed reagins for ragweed and pancreatin. No reagins were found for the other clinically reacting substances.

It should be emphasized that, although inhalation of these allergens was followed by respiratory symptoms, ingestion of large quantities of pepsin, caroid, bile salts, or pancreatin was without clinical effect. The animal source (hog) for pepsin and pancreatin was also ruled out as a factor in allergy since there was no reaction to pork either clinically or by skin tests.

No attempt to desensitize to pepsin was made. When the patient comes into contact with the various offending drugs, he uses wet cotton pledgets in the nostrils, with a wet gauze face mask. This seems to be sufficient to protect him from symptoms.

DISCUSSION

It is a known fact that pharmacists and others who handle drugs not infrequently develop symptoms of vasomotor rhinitis because of sensitivity to these substances. While caroid allergy is not uncommon, there has been no recorded case in the literature of pepsin as a cause of sensitization.

CONCLUSIONS

A case of allergy to pepsin, which produced respiratory symptoms in the form of vasomotor rhinitis and asthma in a ragweed-sensitive patient, is reported.

Ingestion of pepsin was not succeeded by any of the respiratory symptoms noted following its inhalation.

Contact with caroid, pancreatin, and bile salts by inhalation resulted in vasomotor rhinitis, but no evidence of asthma.

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Annual Review

ALLERGIC DISEASES IN CHILDHOOD

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THE following summary of recent articles relating to allergy in pediatrics cannot hope to be complete. It represents a brief review of those writings to which the author has had access and which have come to his notice. It is hoped that in many instances it will serve to call the reader's attention to subjects which he will want to read in the original.

One of the problems in pediatrics which is often difficult to decide is the answer to the question: Is a tonsillectomy and adenoidectomy indicated? The problem becomes only more complicated when a known allergy enters into the picture. One wishes, on the one hand, to avoid useless surgery which may not only fail to relieve the condition for which it was undertaken, but also actually initiate or aggravate asthma which has previously been mild and occasional. On the other hand, real indications for adenotonsillectomy may be present in the allergic person and symptoms may exist for which the only proper and satisfactory treatment is surgery. There is no doubt that in a given case it is often a difficult matter to try to differentiate the component elements of the picture.

Piness and Miller,[1] defining allergy as "a nonsurgical disease," find that in a large group of asthmatic children who had undergone tonsillectomy, 43 per cent had done so on the advice of a physician for the relief of asthma. Their continued presence in the allergy clinic indicated the insufficiency of the relief. In 17 per cent of the total group of allergic children, tonsillectomy was credited with having initiated the first frank allergic symptoms. Piness and Miller consider lymphoid hyperplasia one of the distinctive features of allergy, and, therefore, enlarged tonsils and adenoids as characteristic. They feel the enlargement is often incorrectly interpreted as a sign of infection.

Every allergist and pediatrician has had ample opportunity to confirm much of what these authors point out. It would seem, however, that if the enlargement is sufficient to cause obstruction, early success in effecting a reduction in size by the allergic approach would still be the only alternative to operation. Cohen[2] feels this can often be accomplished.

All the warning against ill-chosen surgery does not come from the allergists. Hansel and Chang[3] and Gittins[4] repeat the warning as otolaryngologists, as does Barnett,[5] a pediatrician.

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In his article on the differential diagnosis of headache Gittins[4] calls attention to the frequency of migraine in children and its independence of sinusitis, with which it is often confused. Lima[6] finds allergy to be the chief etiologic factor in migraine in children, and foods frequently responsible. Hill[7] also finds food allergy to be the cause of migraine in children, often enough of a cause to warrant investigation of the possibility in every case. In a small number of cases, the author has also found food allergy to be the chief factor in bilious, sick headaches. It seems to be true, as Gittins[4] points out, that often the parent does not know of the headache as the child does not complain of it. Other symptoms, particularly the gastrointestinal ones and fever, receive most of the attention. A broad definition of migraine attacks is intended.

MILK ALLERGY

Cow's milk will always have a prominent place in the discussion of allergic problems in pediatrics. Its importance in growth and nutrition has given it a key position in the case of allergic infants and children. Hill[8] states that a person may become sensitive to either of two fractions in cow's lactalbumin, one species-specific, the other not, and that, in addition, he may become sensitive to casein. He tested forty-four eczematous infants who gave a positive intradermal reaction to cow's lactalbumin with a solution of goat lactalbumin of the same strength. Ten were entirely negative to goat lactalbumin, nine gave doubtful reactions, and twenty-five gave identical positive reactions to both. This would at first make it seem that ten, possibly nineteen, of the forty-four infants might do better on goat's milk than on cow's milk. Unfortunately, about half of the group were also sensitive to casein from both species. This would theoretically halve the number in whom benefit could be expected upon a change to goat's milk. Furthermore, Hill states that heating decreases but does not eliminate antigenicity of the three milk fractions. Clinically, goat's milk proves to be of more value than heated cow's milk, but more often than not it fails to solve the problem of milk sensitivity.

Ratner[9] has decidedly different views, as he has stated before. He believes heating evaporated milk renders it so nonantigenic that, in the majority of cases of milk sensitivity, it is well tolerated, and that, therefore, there is little need for substitutes. He supports his statements with evidence afforded by guinea pig sensitization studies. Interesting and valuable as these studies are, it is apparent that they do not have direct clinical application in the numerous children in whom heated evaporated milk is capable of causing allergic symptoms. Clinically, also, certain precooked cereals[10] and even cereal-derived sugars[10, 14] are capable of causing allergic symptoms, although Ratner's[11] work with guinea pigs indicates that, on theoretical grounds, this should not be so.

Hill[8] also believes that there is a group of infants without eczema who are milk-sensitive and who seem to be allergic to the species-specific fraction alone. It includes the relatively few infants who are shocked in anaphylaxis-like fashion early in life by cow's milk. More often than not their skin tests are negative. Goat's milk is well tolerated by this group.

Possible disadvantages of heating human milk are mentioned by Weingartner.[12] He showed that heating breast milk reduced its calcium and its phosphorus contents about 20 and 30 per cent, respectively. A corresponding reduction did not occur when cow's milk was heated. An organic and inorganic acid and phosphorus combination was assumed to be responsible.

As was perhaps to be expected in the light of the problem of cow's milk allergy, Robinson[13] found that breast-fed babies had fewer rashes of all types, including eczema, and less diarrhea than artificially-fed babies.

Levin[14] reports 77 per cent of eczematous infants clinically sensitive to milk, although in only two-thirds was the sensitivity associated with a positive skin test.

INFANTILE ECZEMA AND DERMATOLOGY

The problems confronting the pediatrician caring for infantile eczema are numerous. Apart from those which are obvious to him, there would seem to be hidden ones lurking in the background. Hellier[15] and Virasoro and Ugarte[16] mention a meteorologic and climatic factor. Davis[17] records his unfortunate loss of three consecutive cases in which sudden unexplained death occurred. All were hospitalized patients, a factor he considers important. Asperger[18] mentions the danger of vaccinating siblings of children with eczema. A 9-month-old eczematous infant died of generalized vaccinia acquired from her 12-year-old brother.

Hansen[19] has extended his studies of fatty acids in eczema to the phospholipid fraction. He finds this fraction more unsaturated and of higher molecular weight than the total fatty acids. However, he continues to find that in normal infants both phospholipid and total fatty acids are more unsaturated than they are in the infantile eczema group. Care was taken to rule out the influence of diet, fever, and topical applications.

Sharlit[20] reports definitely increased excretion of indoxyl in the urine of infants with dermatoses, chiefly eczema. He believes it is due to intestinal stasis and indicates inordinate putrefaction of protein in the intestine.

In the treatment of infantile eczema, Levin[14] finds milk elimination important in three out of four cases. He advocates a liquid soybean substitute. In contrast with usual practice, he believes a water bath

with baking soda and without soap beneficial and advises it several times a week. In common with Hecht[21] and others, he stresses environmental control as for the asthmatic patient.

Certainly there is much to be said for avoiding dietary restrictions as much as possible in infancy. Illustrating the point, Clement and co-workers[22] report an instance of avitaminosis A with severe xerophthalmia in an infant being treated by dietary means for eczema. Too often an important food is eliminated as a trial, only to remain out of the diet beyond the trial period even though there is insufficient proof of the need to do so. Levin[14] finds that, in the majority of instances, there is a rapid acquisition of tolerance to milk so that it can be added as evaporated milk within from six to twelve weeks. The reviewer feels that it should be a rule to prescribe calcium and phosphorus in powder or tablet form whenever milk is eliminated. Then if the unforeseen happens, such as the failure of the patient to report back during a long period of elimination, these important minerals will have been prescribed.

Albert and Walzer[23] report an unusual type of skin response to patch testing with an ointment composed of three parts of petrolatum and one part of defatted powdered antigen. The materials tested included silk, feathers, orris root, ragweed pollen, timothy pollen, plantain pollen, cottonseed, cow epithelium, goat epithelium, tobacco, sheep's wool, wheat, milk, egg, and corn. Allergic children gave the majority of positive tests, whereas the incidence in allergic adults and normal children was quite low. Reactions were not more numerous in the children with cutaneous allergy as compared with other types of allergy. The reaction was chiefly vesicular with very little erythema, appeared in from one to seven days, and was followed by desquamation. Half the allergic children tested were positive by this method to feathers and silk; other allergens gave reactions less frequently. Calling to mind the report of Peck and Salomon[24] several years ago on patch testing eczematous children with moist powdered allergens or allergens in solution, this report differs in several respects. The reaction described by Peck and Salomon was characterized by papule formation and considerable erythema, occurred chiefly in children under 5 years of age, and included reactions to egg, wheat, and milk. The reactions described by Albert and Walzer differed in appearance, occurred chiefly in children from 5 to 12 years old, and included no reaction to egg, wheat, or milk.

Not the least interesting and important finding was that hypersensitiveness was induced in some of the children by repeated application of certain of the allergens. This induction of sensitivity will always be a matter to be weighed in patch testing. Albert and Walzer make no clinical interpretation of their findings at the present time.

A different type of induced sensitivity is that reported by Flahiff,[25] who found tuberculin sensitivity was usually induced by intracutaneous

inoculation of heat-killed tubercle bacilli of a highly virulent strain in the inmates of a boys' reformatory school. The clinical application of this finding is suggested by a report by the same author following the above report, indicating that tuberculosis is more readily acquired and more often fatal in adults with a negative tuberculin test than when the test is positive. The advocates of a positive tuberculin test now have this additional evidence to add to their arguments.

In a study of the pH of the skin surface on the arms of normal children, Blank[26] finds wide variation between 4.0 and 7.0. There is little difference between children and adults, but males tend to average lower than females. Adult females were shown to vary widely from day to day. Although, as stated, there was wide individual variability, the antecubital area was rather consistently the most acid area on the arm. These are interesting basic studies, the interpretation of which awaits further work and additional normal standards. It will be interesting to see whether the popliteal areas and other areas favored by infantile eczema share this acid characteristic with the antecubital area.

BODY AND PERSONALITY CHARACTERISTICS

A quite different aspect of eczema is that studied by Bakwin and Bakwin,[27] who find that eczematous infants have, on the average, a wider head, broader face, more widely separated eyes, and a larger body circumference than are found in a control group. In addition, they are slightly taller and considerably heavier. Males outnumber females two to one in their series.

Apart from this inherited body type associated with a type of allergy, Milton Cohen[28] stresses the acquired changes which were mentioned in the last two reviews.[29] Stanley Cohen[30] and Felts[31] also point out the interference with growth which results from allergic diseases. Improper facial growth is of particular interest chiefly as a factor for consideration in the etiology and treatment of orthodontic deformities.

Felts discusses chest deformities associated with asthmatic emphysema. Francis[32] finds epiphyseal ossification a more delicate objective indication of constitutional health than height and weight. He reports that gastrointestinal sensitivity as shown by mild eczema, even when so well controlled that no retardation of growth occurs, will retard epiphyseal ossification. There are numerous other influences over the degree of epiphyseal ossification, one of them being the amount of available mineral in the diet. Since cow's milk has more minerals than breast milk, bottle-fed babies have a more advanced epiphyseal rating that breast-fed babies. It has also been shown that there are racial and sex differences in ossification during the period of infancy, and Bruch[33] has discussed the variation in ossification associated with obesity. Such a variety of influences would present difficulties in the clinical use of epiphyseal development as a measure of allergic control.

A recent report on the personality of the allergic individual is that of Riess and de Cillis.[34] They studied a large group of children with various types of allergy and concluded that, as a group, they were more ascendent, more extroverted, and more unstable emotionally than normal controls. The combination of extroversion and emotional instability does not often occur together in normal children, and in this respect the allergic subjects appear to have an unusual "personality constellation." Children with skin allergies exhibited this personality trend more than did those with vasomotor rhinitis, asthma, or mixed allergy.

A detailed study of the personality of a child with neurodermite is given by Ackerman.[35] Since the child was a half-orphan and had been raised in an institution, the case does not lend itself well to the study of personality in neurodermite. These studies are added to many recent ones on the subject of personality trends in allergic children which have been discussed in recent critical reviews.[29]

PREVENTION OF ALLERGY

Donnally[36] discusses the prevention of food allergy, his concept of the matter being very similar to that of Ratner, with its attention to intrauterine and breast milk sensitization and avoidance of raw foods during the neonatal period and during convalescence from disease. Rosenbaum[37] also suggests attention to the same factors to prevent sensitization. While the matter here, as far as the fetus is concerned, is largely one of passage of antigen through the placenta, the passage of skin-test antibodies (reagins) is also of great moment. Wiener and Silverman[38] have determined a "coefficient of distribution" of certain antibodies between maternal and cord blood. They find that for hemagglutinins and syphilitic reagin the ratio of titers in the maternal blood to the corresponding antibody in the cord blood is relatively constant and falls between 8 and 16. This index of permeability of these antibodies may or may not hold for other antibodies. In particular, it would be interesting to know whether there is such a figure for skin-test antibodies. As the authors point out, the presumed affinity of reagins for tissue cells may greatly alter their chances of reaching the fetal circulation. Zohn[39] and Bell and Eriksson[40] failed to demonstrate the passage of skin-test antibodies to the fetus.

VITAMIN C AND IMMUNOLOGIC ASPECTS

A totally different approach to the problem of preventing allergy is that of Shaw and Thelander.[41] They feel that vitamin C may protect against sensitization. The mechanism is not entirely apparent, but it seems plausible, they feel, that lack of vitamin C may conduce to a more intimate exposure of the cells to foreign protein in the circulation. They have had less colic, which they take to indicate allergy, in infants since they have made a practice of giving ascorbic acid daily early in

the newborn period. They do not believe the protection rests on the basis of rendering the gastrointestinal tract less permeable to unaltered protein. Bronfenbrenner and associates,[42] on the other hand, believe that if vitamin C plays a part in human allergy, it is not by any direct effect on the process of sensitization, but because of its ability to repair a lesion in the gastrointestinal tract which is due to deficiency in C and which results in the increased absorption of unaltered protein. They found that guinea pigs suffering from a deficiency in vitamin C were more easily sensitized by way of the gastrointestinal tract and that they could also be shocked more easily by the oral route. Increased permeability of the alimentary tract was taken to be the factor which accounted for both of these findings. Diehl[43] presents evidence that, when the intraperitoneal method of sensitization is used and the shocking antigen is given intracardially, vitamin C has no effect on anaphylaxis in the guinea pig. He had four series of animals, the first of which received almost no vitamin C, the second of which received larger but still insufficient amounts, and the third and fourth of which received an ample quantity intramuscularly and in their diet, respectively. The highest incidence of anaphylactic death occurred in the second series receiving relatively insufficient amounts of vitamin C; whereas the first and last series, representing the most deficient and the most adequate diets, gave essentially similar results.

It will be recalled that Cohen[44] had previously shown that in a carefully controlled experiment with guinea pigs intracutaneous sensitization was not influenced by vitamin C, whereas Sulzberger and Oser[45] had arrived at an opposite opinion.

While it does not exclude any of the different viewpoints on the question of the role of vitamin C in the induction of sensitivity or the production of anaphylactic shock or allergic symptoms, it is nonetheless interesting to mention that more than one observer,[14] including the reviewer, has noticed clinical sensitivity to cevitamic acid itself, at least as dispensed in tablet form.

Of considerable interest is the report of Tumpeer and Rubens,[46] who showed an inhibiting effect on reagins in pooled sera similar, apparently, to the effect of pooling on hemagglutinins reported by Levinson and Cronheim.[47] Illustrating the possibilities involved in the absence of pooling is Garver's report[48] on clear-cut passive sensitization, as shown by skin test, in several recipients of transfusions from single allergic donors. Waldbott[49] and Rosenbaum[50] both suggest skin testing the recipient with the donor's blood prior to transfusion. From the reagin standpoint this would appear unnecessary with pooled serum, and in any case would seem confusing rather than helpful. Tumpeer and Rubens found numerous immediate reactions to the injection of serum which they thought might be due to food allergens in the recipient's blood stream and to reagins in the donor's, but were more likely due to an irritative phenomenon not dependent on allergy. Two of their cases reacted to their own sera.

The protection of children against diphtheria has afforded two interesting studies in the past year. Thelander[51] has shown the great variability which can be expected in immune response as measured by one method, the measurement of the diphtheria-antitoxin titer following toxoid injection in a group of children and adults. In sixteen adults the antitoxin titer varied from 0.004 to 3 units per cubic centimeter of serum, and in nineteen children a variation of from 0.04 to 4 units was found six months after a uniform administration of toxoid. A detailed study on several persons in the group showed a tendency for a winter and spring rise of antitoxin. The level at which a Schick test became negative in this study was between 0.01 and 0.005 unit of antitoxin per cubic centimeter of serum, whereas Duffy and Mitchell,[52] in a study of Schick tests on patients with scarlet fever, found the border line at about 0.002 unit. Hillman and Linde[53] have studied the Schick test following toxoid in a large number of infants. They report a 25 per cent reversal from a negative Schick test to a positive one within a period of approximately four years following two doses of toxoid. This failure to maintain a negative Schick test is becoming increasingly apparent as large groups of older children are retested. One factor involved, and brought out in this study, is the inadvisability of starting immunization against diphtheria while the mother's passive immunity is still present, a period usually estimated from six to nine months. It is also advised that for routine use three doses of toxoid be given instead of two.

EOSINOPHILIA

Under the title, "Transitory Lung Infiltrations Associated with Eosinophilia (Loeffler's Syndrome)," Smith and Alexander[54] report the case of a 7-year-old girl with transitory lung shadows revealed by roentgenogram and a blood eosinophilia of from 30 to 54 per cent. The scattered and changing shadows were found for two weeks and then disappeared. The child was febrile, and bronchopneumonia had occurred a month previously. The usual causes of eosinophilia were ruled out. The tuberculin test, frequently reported positive in Loeffler's syndrome, was negative. The acceptance of this case as representing what has frequently been reported abroad as Loeffler's syndrome is complicated by the fact that within a month the child developed a fatal streptococcus septicemia. If this is Loeffler's syndrome, it is one of the few instances reported in this country. The etiology of Loeffler's syndrome is disputed. Eversbusch[55] believes it is frequently an allergic edema around old tuberculous foci, activated by a nontuberculous infection. In the case described above, that explanation would appear to be ruled out by the negative tuberculin test.

Malmberg[56] reports a family in which four members had an unexplained eosinophilia of from 6 to 26 per cent. None of the usual causes of eosinophilia could be demonstrated. He found thirteen other instances of familial eosinophilia in the literature.

Becker[57] mentions the frequency with which an attack of asthma is associated with a fall in blood eosinophilia only to be followed by a rise following the attack. Others, including Piness[58] and the reviewer, have observed this many times. Dalton and Selye[59] report a similar decrease and subsequent increase in blood eosinophilia during the "alarm reaction" in rats and rabbits. The alarm reaction is the response to a variety of damaging stimuli, in this instance the injection of 4 per cent formaldehyde.

OTHER STUDIES

Köhler and Mai[60] studied 111 infants with spastic bronchitis in an effort to determine its relationship to true asthma. A final word was not possible inasmuch as sufficient time had not elapsed in the majority of cases. However, a family history of asthma was obtained in 62 per cent of the group as compared with 22 per cent in a control series of normal infants. No difference in the response to ephedrine was noticed in those with a family history of asthma and in those without such a history. Half the group had been followed nine years. In all, twelve cases of true asthma had developed in the entire group at the time of writing.

This would seem less than one would expect if the majority of cases of spastic bronchitis in these infants were allergic in origin. It would appear wise to adopt a conservative attitude in making a prediction of the eventual outcome of such cases.

Fries and Zizmor[61] report on the clinical symptoms associated with the barium-administered food allergens in children whom he had previously discussed from the roentgenographic standpoint. As was perhaps to be expected, oral administration caused nausea, vomiting, and abdominal pain, and rectal administration caused pain, tenesmus, and nausea. Some severe reactions followed rectal absorption of antigens and led to the discontinuance of this part of the study. Some of the variations, not due to allergy, which can be expected in such a study from the roentgenographic standpoint are indicated by the report of Macy and her collaborators[62] on normal variations in gastric emptying times with mixtures of barium with water and with pasteurized, evaporated, and base-exchanged milks. The water-barium mixture left the stomach quickly, whereas the milk mixtures were much slower. Pasteurized milk took slightly longer than either evaporated or base-exchanged milk.

TREATMENT OF ASTHMA

Crump[63] reports on a five-year study in which 223 consecutive children with asthma were bronchoscoped. Of these, 112 were in regular attendance at the clinic for six months or more and received treatment with autogenous vaccine obtained by bronchoscopy. This procedure had revealed a purulent tracheobronchitis in seventy-two children, and in

thirty-three cases there was either early evidence of dilatation or definite bronchiectasis. In two, the bronchi were seen to collapse partially with inspiration. Only four were found to have normal bronchi. Bronchial infection was thought to be far more frequent in asthmatic children than in asthmatic adults. Nearly every case had a history indicating that the asthmatic attacks came on in relation to a "cold."

The vaccine treatment consisted in weekly subcutaneous injections of increasing doses, to a maximum of from 500,000,000 to 2,000,000,000 organisms. Asthma developed within twelve hours of administration of vaccine in eleven cases. Exact interpretation of results is difficult, as, in all save twenty-seven cases, numerous other procedures were carried out. In these twenty-seven, complete relief was obtained in twenty-three.

One cannot help recalling that the usual history of asthma in childhood is that "colds" precede the attack, but that these "colds" usually prove to be attacks of allergic rhinitis caused by the same nonbacterial allergens which produce the subsequent asthmatic attack. It is also a possibility that nonspecific shock was a factor in the improvement reported.

One of the surprising things about this report is the high incidence of purulent tracheobronchitis found and the fact that no mention is made of mucus plugs which are usually thought to be an important part of the pathology of asthma. Chronic infection is commonly thought to occur with considerably greater frequency in adults with asthma than in children with asthma.

In contrast with the majority of published results to date, Abt[64] reports striking improvement in the treatment of twenty children suffering from hay fever, asthma, allergic rhinitis, and sinusitis, with oral potassium chloride. The best results were in those patients, nine in number, who had both hay fever and asthma. As is mentioned in a footnote in the report, the results of a treatment of hay fever begun in mid-October in Chicago cannot be considered significant.

Stoesser's report[65] stresses the importance of environmental control in childhood asthma. He finds that inhalants other than pollen are the most common cause of asthma in this age period and that hyposensitization is disappointing. On the other hand, environmental control gives satisfactory results.

In Germany, Frick[66] and also Becker,[57] who discusses her experience with allergic cases over a five-year period in a children's hospital, find food allergy of secondary importance to inhalant allergy.

In common with these authors, the reviewer has felt that the control of the household environment was the most frequently neglected and most important procedure in treating asthma in childhood. Salen and his co-workers[67] appear to have arrived at the same opinion in studying a group of thirty-six school children in Stockholm. In these children, all from 8 to 14 years old, previous care, chiefly medical in nature, had been quite disappointing. Investigation pointed more to

house dust than to any other factor. As it seemed impossible to control house dust in the overcrowded homes from which the children came, twenty-two of them were quartered in a former schoolhouse which was as dust-free as possible. Afternoon visiting at home was permitted. The improvement in attendance at school and freedom from asthma was remarkable. Consequently the home, first started as an independent project, was taken over as a civic project by the city of Stockholm. While recognizing the numerous other factors which may have been involved, Salen feels that control of house dust was by far the most important one. There are many allergists and pediatricians who have longed for such a children's home, even for temporary use.

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Society Proceedings

Vascular Allergy in the Pathogenesis of Bronchial Asthma With Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis.*

JOSEPH HARKAVY, M.D., New York, N. Y. (Abstract.)

This report deals with a study of eight patients, seven of whom had typical bronchial asthma and one, bronchospasm and cough. The exciting factors in two of these patients were confirmed clinically as due to synergistic sensitization to pollens, foods, and bacterial products emanating from chronic sinus infections. In the remaining six, bacterial hypersensitiveness in the presence of sinus disease was the only discoverable etiological factor.

The major attacks of asthma were associated with recurrent migratory inflammatory interstitial lesions in the lungs, with sputum eosinophilia, and also with reactions in the serous membranes characterized by pleural effusions in six patients, and peritoneal exudates as well as pericardial involvement in three out of the eight patients.

The aspirated fluids were sterile and contained eosinophiles up to 100 per cent.

The pericardial reactions took the form of an acute pericarditis which reverted to normal within three weeks in one case and progressed to a chronic adhesive stage in two others.

Coincidental with the asthmatic attacks and the pleuropulmonary involvements, there appeared electrocardiographic abnormalities in the deflections and amplitudes of the T-waves and QRS complexes. These returned to normal with the termination of the asthmatic seizures in four patients and remained permanent in two patients who ultimately died.

Other important features consisted of an increase in blood eosinophilia in all cases, at times elevated to 84 per cent; fugitive polyarthritis and polyneuritis in three cases; hemorrhagic necrosis in the thigh in one case; and urticaria, angioneurotic edema, and purpura in two patients, one of whom also developed subcutaneous nodules.

Biopsies of the skin lesions and a subcutaneous nodule disclosed perivascular eosinophilic infiltrations. In addition to the latter, the subcutaneous nodule also showed areas of periarteritis nodosa.

Bone marrow sternal puncture gave evidence of a marked increase in eosinophilia.

The presence of eosinophilia in the sputum, in the serous exudates, and in the perivascular infiltrations in the skin, together with the periarteritis nodosa in one of the cases, implies active involvement of the

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vessels of the lungs, serous membranes, and cutaneous tissues which was responsible for their increased permeability and permitted the passage of the eosinophile cells. It would thus seem reasonable to assume that the interstitial pulmonary infiltrations noted on x-ray examination, accompanied by sputum eosinophilia which appeared and disappeared simultaneously with the exudates in the pleura and electrocardiographic changes, were probably also caused by perivascular eosinophilic exudates similar to those noted in biopsies of the skin.

In view of the fact that the asthmatic paroxysms ran a parallel course with the pathologic lesions in the lungs, it may be inferred that the former were an expression of the allergic reactions of the vessels in the lungs and bronchi primarily, as part of a generalized vascular and mesodermal response to allergenic stimulation simultaneously occurring in the other shock organs. These observations give rise to the concept that the underlying shock tissue of bronchial asthma in these, as well as probably in other, cases lies primarily in the blood vessels of the bronchi, the lungs, or of both, rather than in the bronchial mucosa. Sensitization of these vessels results in increased permeability and leads to passage of antigen, which in turn sensitizes contiguous structures, such as the bronchial mucosa, glands, musculature, etc. The resulting edema and concomitant inflammatory eosinophilic exudate which infiltrates the muscles of the bronchi probably account for the so-called "muscle spasm." In cases of long duration the additional labor imposed upon the bronchial musculature in expelling the air and increased viscid secretions out of the inflamed bronchi may be regarded as responsible for the hypertrophy described by Huber and Koessler.

The participation of the blood vessels of the serous membranes in the allergic responses, together with the cardiac involvement, resulted in the clinical picture of mediastinopericarditis which returned to normal in one case, and in constrictive pericarditis with subsequent progression to polyserositis in two others. This would suggest that these syndromes were the sequelae of hyperergic vascular reactions in serous membranes and the myocardium. On the basis of these findings, the following hypothesis seems reasonable. Just as the asthma may be regarded as a manifestation of sensitization of the blood vessels and of other mesenchymal structures in the lung, so might the symptom complex of constrictive pericarditis or polyserositis in persons without a frank allergic background or the tendency toward eosinophilia likewise represent hypersensitiveness of serous membranes in nonatopic persons to some fundamental infection. Absence of eosinophilia does not exclude allergy.

The presence of eosinophiles in the perivascular infiltrations in the skin biopsies in two cases, as well as in certain areas of the subcutaneous nodule in one case, which likewise contained blood vessels

in various stages of involvement going on to periarteritis nodosa, testifies to their allergic nature and strongly supports the view that periarteritis nodosa represents a hyperergic vascular response.

Demonstration of an increase in eosinophilia, as well as in the total number of white blood cells in the bone marrow, indicates that the latter participated as a specific shock organ.

DISCUSSION

From the observations recorded above it may be inferred that the various manifestations under discussion represent responses in different shock organs in which sensitization of blood vessels and associated mesenchymal structures played the determining role. It is evident that, in the moderately hypersensitive person, allergic reactions in the lung may be expressed by bronchitis and cough; and in the person with increased sensitivity, by paroxysms of asthma. Either of these conditions may disappear completely under causal therapy, without leaving any visible pathologic changes. They may be regarded as reversible reactions characteristic of most of the simple and readily controlled manifestations of hypersensitiveness. In the more severe types of polyvalent sensitivity, especially where bacteria assume a dominant as well as synergistic role in conjunction with other excitants, allergic inflammation in mesodermal structures may become more extensive and profound, in so far as it is augmented by the destructive effect of bacterial toxins.

Not only the bronchi, but other portions of the pulmonary tree, as well as the myocardium, pleura, pericardium, peritoneum, and hemapoietic system may be involved. Under such circumstances there arise distinct syndromes which may likewise be reversible or irreversible, the allergic nature of which may be recognized by the asthmatic component and eosinophilia. The number, character, and variations in the combinations of the shock tissues involved determine the clinical picture. Thus, there may be a pulmonary myocardial complex, a pleuropulmonary myocardial response, or a pleuropulmonary myopericardial response resulting in the picture of constrictive pericarditis. Finally, with the extension of reactions to all of the serous membranes, the characteristic picture of polyserositis becomes apparent. Superimposed upon these fundamentally allergic responses, disturbances in the dynamics of the circulation are inevitable. Although these symptom complexes seem to be clinical entities, it should be emphasized that they are not of an essentially independent origin, but are merely varying expressions of a state of hypersensitiveness. The identity in their basic mechanism, despite variations in the clinical pictures, supported by the pathologic findings in the biopsy sections, especially in one of the cases in which were seen gradations from simple perivascular, eosinophilic infiltrations such as were pres-

ent in two other cases to the full picture of periarteritis nodosa, suggests that the cases reported herewith represent hyperergic vascular responses milder in degree, but similar to those in periarteritis nodosa. They may be regarded as early stages or potential types of this disease.

DR. HARRY L. ALEXANDER, St. Louis.—At the meeting of the Association of American Physicians two weeks ago in Atlantic City, Dr. Rackemann presented the report of a series of cases which, if not identical with these, went further than these and proved to be periarteritis nodosa. We would be interested if Dr. Rackemann would comment on this presentation.

DR. FRANCIS M. RACKEMANN, Boston.—At that meeting we presented a study of eight patients, four of whom died, and in connection with my own paper this morning, I thought I would throw on the screen the same slides we had there because they fit in with other remarks I want to make later.

Now, in connection with that study, Dr. Greene reviewed the literature of periarteritis nodosa with some care. He found that the whole literature contains 245 references to individual cases. Of those 245 cases, asthma occurred in something less than 10 per cent, and a high eosinophilia, that is, over 25 per cent, occurred in only about 14 per cent.

Now, when we began to find our special cases in Boston, everyone jumped at the conclusion that a high eosinophilia was an important and perhaps necessary part of the picture, if the true diagnosis was to be periarteritis nodosa. Dr. Greene's study of the literature has, of course, upset that idea, and now we recognize that periarteritis nodosa can occur without eosinophilia. In the same way, we must recognize that periarteritis nodosa can occur without asthma and, of course, without either asthma or eosinophilia. So it would seem to me very doubtful if there is sufficient evidence at the present time to say that periarteritis nodosa is an allergic disease. Perhaps it is, but I do not believe there is really any particular evidence to confirm such a hypothesis.

In the meantime, however, I should like to give you the conclusions which we presented at Atlantic City. They were these: When a patient has severe asthma, pains and numbness in his extremities, which seemed to be a very characteristic clinical symptom, and evidence of local lesions in the blood vessels, with resulting hemorrhage from the lungs, kidney, stomach, and in the superficial blood vessels with purpura, and, finally, where there is eosinophilia which is over 25 per cent, it is our conclusion that in such a case the diagnosis is probably periarteritis nodosum, and we are certainly justified in thinking that the prognosis is serious.

DR. MILTON B. COHEN, Cleveland.—It seems to me that the conclusions expressed by Dr. Rackemann can well be brought together if, instead of thinking of periarteritis nodosa, we think of the pathology of the allergic states in general. An allergic reaction may be one which is completely harmless and reversible or one which is irreversible and produces tissue damage. If tissue destruction occurs there is going to be some trouble, and if there is enough trouble in one area, there will be symptoms referable to that area.

Dr. Rackemann is correct in the statement he makes. Not all of these cases are allergy of the usual clinical type. That does not mean that they may not be allergy in the broad sense.

The significant thing, it seems to me, about all of these cases—and I think Dr. Harkavy is to be congratulated for putting together such a large group—is that the allergic patient, the kind you and I are going to see, who has any evidences of anything which might possibly be explained on the basis of a lesion in the blood vessel, which is diminishing blood supply to some organ or part, should be considered a case of periarteritis nodosa until proved otherwise. Then we will not be disappointed by giving a case a prognosis which ultimately will distress us very much.

Dr. George L. Waldbott, Detroit.—I, too, feel that what Dr. Harkavy has described today is a definite clinical picture distinctly different from bronchial asthma and its usual complications.

I have seen two such cases within the past few years. One of the patients had been very carefully studied at the University Hospital in Ann Arbor where, because of a white blood count ranging above 65,000 and an eosinophile count as high as 75 per cent, the diagnosis of a leucemic disease had been made. Possibly the patient was not studied in the allergy department because of the very apparent outstanding hematologic features. The prognosis given to the patient's family was extremely bad.

When this patient came under my care I at first hesitated to treat him because of the extensive pulmonary infiltration which I felt was associated with the hematologic condition. Because of the suggestive history, however, I placed the patient on allergic management, and, to my great surprise, the condition cleared up entirely.

Dr. George Piness, Los Angeles.—The paper presented by Dr. Harkavy today brings to my mind a report made by us about two years ago in which we found conditions similar to those brought to our attention today, with the exception that the conditions were reversible instead of irreversible. The x-rays presented this morning were also similar to those published in this series of children mentioned previously. As I glance at them, there appear to be some areas of atelectasis. Another observation was that most of the lesions presented by Dr. Harkavy were quite like those presented by us in that they were usually on the right side of the hilus region.

The leucocyte counts in both groups were comparable, usually being high and with a definite drop to the normal when the condition cleared up.

In the group presented, practically all gave a history of sinusitis, and, if the assumption that they are allergic persons is true, then the sinusitis might have been the primary allergic manifestation since it is true that allergic persons are predisposed toward acquiring secondary sinus infections. Therefore, this observation would be of very little significance, merely pointing out that they acquired a secondary infection on an already allergic mucous membrane.

Dr. Rackemann's remarks that the literature showed such a small percentage (10 per cent) with history of allergy, shall we say, or asthma, in cases of periarteritis nodosa are not in accord with the literature we recently reviewed, particularly the work done at Mount

Sinai Hospital by Dr. Young who showed a much larger percentage of asthma in his cases. In cases observed by us there was usually a history of asthma, but whether or not it was a true bronchial asthma of the allergic type I am not in a position to say.

In the group of cases reported by us in children, the course was usually acute and reversible. I have not been convinced that the cases reported this morning are purely allergic in their etiology.

DR. HARKAVY.—I wish to thank the gentlemen who discussed my paper for their interesting comments.

In answer to Dr. Rackemann's statement in respect to the fact that, since only 10 per cent of asthmatics have been found among patients with periarteritis nodosa, it is a question of whether or not periarteritis nodosa should be regarded as allergic in nature, I should like to make the following remarks:

As a rule, most of the cases of periarteritis nodosa which one meets and recognizes in practice have as their major symptoms malignant hypertension with renal insufficiency. Other less frequent manifestations of periarteritis nodosa which go undiagnosed, unless superficial nodules or renal complications are present, may be referable to the cerebrospinal system, where they simulate brain tumor or polyneuritis; to the heart, when they look like the usual cases of coronary artery disease; to the liver or gall bladder, in which instances a diagnosis of gallstones or hepatitis is made.

THE AMERICAN ASSOCIATION FOR THE STUDY OF ALLERGY

Resolutions

WHEREAS, the American Association for the Study of Allergy has learned with deep regret of the death of Dr. Isidor Harrison Tumpeer, and

WHEREAS, the Association has sustained the loss of one of its beloved and honored members, and

WHEREAS, his amiability, enthusiasm, and kindliness were an inspiration to all who knew him, and

WHEREAS, he has made most valuable contributions to the literature in the field of pediatric allergy, be it

Resolved, That we, the American Association for the Study of Allergy, formally and sincerely record the realization of our misfortune in his untimely passing, and be it further

Resolved, That a copy of these resolutions be spread upon the minutes of the Association, that a copy be forwarded to his wife and his family, and that a notice be printed in the JOURNAL OF ALLERGY.

HARRY L. HUBER
ISIDORE PILOT
LEON UNGER

WHEREAS, the American Association for the Study of Allergy has heard of the most untimely death of one of its members, Dr. George Flamm, and

WHEREAS, the Association has suffered the loss of one of its devoted, beloved, and honored members, and

WHEREAS, his amiability, his jovial character, and his personal charm were known and admired by all who knew him, and

WHEREAS, he has made interesting and stimulating contributions in the field of allergy, be it

Resolved, That we, the American Association for the Study of Allergy, formally and sincerely record our great loss and deep sorrow in his untimely passing, and be it further

Resolved, That a copy of this resolution be spread upon the minutes of the Association and that a copy be forwarded to his wife and family.

H. HAROLD GELFAND
GRAFTON TYLER BROWN
AARON BROWN

Dr. Alfred Hans Waring Caulfeild died May 2, 1940, in his sixtieth year. He was born in a small village in Ontario and was educated in Canada, graduating from the Medical School of the University of Toronto in 1904.

His early interest was in tuberculosis, as is shown by the titles of his early papers: "Investigations on Pulmonary Tuberculosis" and "The Effect of Anatomical and Immunological Data Upon Our Conception of the Tuberculous." One can discern his thirst for greater knowledge, and it was natural that the importance of allergic reactions in tuberculosis should lead him to the field of clinical allergy. His approach to medical problems was always original and comprehensive. While other men became surgeons or internists or just allergists, he perfected himself in the diagnosis and treatment of diseases of the chest. He was an internist, a bronchoscopist, and a thoracic surgeon, as well as an allergist, and he was a master in each field. Above all, he was a Doctor.

In 1922 his paper on "Desensitization of Hay Fever Patients by Injection and Local Application" appeared. After that time, allergy seemed to be his chief concern, and his works on the chemical fractions of ragweed, on the transfer of human reagins to animals, on poison ivy, and on contact dermatitis have been important steps in our knowledge. He was a research member of the Connaught Laboratories in the University of Toronto, and he was director of pathology at the Muskoka Cottage Hospital. During the World War he was on active duty overseas with the Canadian Army Medical Corps.

He was a devoted member of the two national allergy societies and took an active part in their meetings. His own presentations were clear and simple, and when he discussed the work of others, his remarks were always pertinent and helpful. To meet Dr. Caulfeild was to make a new friend—a delightful personality. His genial smile and his ready wit made him excellent company. Everyone liked him and respected him. In 1933, he was made president of the Association for the Study of Allergy, and, in 1934, president of the Society for the Study of Asthma and Allied Conditions—the first man to occupy the two chairs.

He enjoyed life, and the world is better for his presence in it. He leaves a wife and a son. The boy is now a member of the 102nd Field Regiment in the British Royal Artillery and he will carry on.

WHEREAS, through the death of Dr. Alfred Hans Waring Caulfeild, the American Association for the Study of Allergy will miss greatly the wise counsel and the friendly influence of a devoted friend and member, be it

Resolved, That the Association formally and sincerely records its great loss, and be it further

Resolved, That this brief memorial note and these resolutions be spread upon the minutes of the Society; that they be printed in the JOURNAL OF ALLERGY; and that copies be forwarded to his family as an expression of the deep appreciation and sympathy of the Association.

RICHARD A. KERN
FRANCIS M. RACKEMANN
LOUIS TUFT

Selected Abstracts

Asthma and Hay Fever

Under the Direction of Samuel M. Feinberg, M.D., and Theodore B. Bernstein, M.D., Chicago

Comparison of Treatment of Severe Asthma by Electrophoresis of Epinephrine With Other Methods. Abramson, H. A.: Arch. Phys. Therapy **21**: 261, 1940.

The author treated a group of fourteen patients with severe asthma by means of electrophoresis of epinephrine hydrochloride, 1 per cent. A single treatment usually consisted of the application to three successive skin areas, each from 30 to 50 sq. cm. in area, and each area being treated for from ten to fifteen minutes. Blanching occurs, which serves to reduce the rate of absorption of the epinephrine from the skin site. The author estimates that an absorption rate of approximately 1 mg. per hour may be achieved with the method outlined. No constitutional reactions were observed in the first thirty-five persons upon whom the electrophoresis technique was used. Also, there was no rise in blood pressure in normal persons.

It was observed that this method gave relief in some patients who had been considered adrenaline fast, and also in some in whom subcutaneous injections of adrenaline caused nervous reactions. During the period of electrophoresis treatment, administration of epinephrine in oil or aminophyllin intravenously could be omitted.

Bronchial Asthma: New Use For an Old Remedy. King, G. S.: New York State J. Med. **40**: 485, 1940.

The author has used intravenous injections of strontium bromide, 15 grains per 10 c.c., for the treatment of the symptoms of asthma, with good results. Many of his patients who had become tolerant to adrenaline, ephedrine, and morphine experienced immediate relief when the drug was injected slowly. The administration of strontium bromide is generally accompanied by a diffused feeling of warmth. The discomfiture is practically nullified if the solution is injected slowly. Usually before the entire 10 c.c. is injected the patient is free of symptoms. If no response is obtained to the first injection, a second or third may be given. The author has never seen an anaphylactic reaction due to the administration of the drug intravenously, other than the local or skin manifestations due to bromide intolerance.

Pollen Asthma and Hay Fever in Children. Copeland, S. C., and Keating, J. P.: Pennsylvania M. J. **43**: 1137, 1940.

This is a clinical analysis of fifty-eight cases of pollen asthma and hay fever in children observed for from one to five years. Only six had pure hay fever; twenty-eight had pollen asthma, and twenty-four had both asthma and hay fever. The age of onset was as early as 8 months, and in thirty-eight children symptoms were evident by the preschool age. A positive past medical history of allergy, as evidenced by asthma, eczema, and urticaria, was obtained in 72 per cent of the

cases. The family history was positive in 55 per cent. The pollen sensitivity was that of trees, grass, and ragweeds. Most patients were sensitive to more than one pollen; 20 per cent were sensitive to ragweed pollen alone, and 6 per cent to timothy alone. The remaining 74 per cent were sensitive to both grasses and weeds. Good results in treatment were obtained in 80 per cent of the cases; the remaining 20 per cent consisted of fair results or failures.

Hemp Pollen Sensitivity in Omaha. Maloney, E. S., and Brodkey, M. H.: Nebraska State M. J. **25**: 190, 1940.

Since hemp was introduced into Nebraska in 1889 in order to produce raw materials for the production of twine, it has grown wild all over the state. Consequently, hemp pollen is an important cause of pollen sensitivity in Omaha, and it is estimated that it constitutes about 17 per cent of the pollen in the air during the fall. The period of pollination of hemp is from early July through August, terminating about the middle of September. The symptoms of the majority of those sensitive start just before the middle of July.

In a series of 119 tested cases, the authors found a total of twenty-eight or 22 per cent, giving positive reactions to hemp. Of these twenty-eight persons, eleven reacted to hemp pollen alone, and seventeen reacted to hemp and other pollen. All of these patients had symptoms of hay fever during the hemp pollinating season. The eleven patients giving reactions to hemp alone had symptoms only during the hemp pollinating season, with no increase in symptoms at the onset of the ragweed season. It was noticed that in these hemp-sensitive persons, both testing and treating had to be undertaken with care, as reactions, both local and general, occurred readily.

Oral Pollen Therapy in Ragweed Pollinosis. A Cooperative Study. Feinberg, S. M., Foran, F. L., Lichtenstein, M. R., Padnos, E., Rappaport, B. Z., Sheldon, J., and Zeller, M.: J. A. M. A. **115**: 23, 1940.

A cooperative study on the question of the oral treatment of ragweed pollinosis was carried out by the allergy clinics of four medical schools—University of Illinois, Northwestern University, University of Michigan, and Rush Medical College. A total of 130 patients with hay fever or asthma were given ragweed pollen in capsules, in most cases, beginning with doses of 500 pollen units and reaching a maximum dose of from 120,000 to 240,000 units. In some instances doses as high as 540,000 units were reached. The treatment in the majority of cases was given preseasonally. Control groups received either placebo capsules, injections of normal salt solution, or standard hypodermic pollen therapy. Although 29.8 per cent of the group receiving oral treatment displayed some degree of benefit, 21.9 per cent of those receiving placebo capsules were also benefited. Gastrointestinal reactions were frequent. The conclusion is reached that the therapeutic effectiveness of oral pollen therapy is, at the highest estimate, of a minor grade, particularly in the control of asthma.

Histaminase in the Treatment of Hay Fever. Keeney, E. L.: J. A. M. A. **114**: 2448, 1940.

In a group of fifteen ragweed hay fever patients during the 1939 ragweed season, histaminase, in doses of from 45 to 75 units daily, was administered orally. In none of the patients was there any degree of relief other than that attributable to fluctuation in atmospheric pollen concentration. Preseasonal quantitative intracutaneous tests were made with histamine and compared with the reactions obtained when histaminase therapy was terminated. In none of these patients was there an appreciable change in the histamine reaction.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

A Case of Dermatitis from 9-Bromo-Fluorene and a Peculiar Reaction to a Patch Test. Cavendish, A.: Brit. J. Dermat. **52**: 155, 1940.

A chemist developed a generalized dermatitis while working with fluorene and derivatives. Patch tests revealed a positive reaction only to 9-bromo-fluorene. Three control patients were tested with this substance (100 per cent as a powder). All three showed slight redness at the test site after twenty-four hours. However, two of the three controls developed late reactions after eight and thirteen days, respectively.

[EDITOR'S NOTE: Such delayed reactions probably represent sensitization by the test application of the substance, with spontaneous flare. Under these circumstances, extreme care should be exercised in performing patch tests with 9-bromo-fluorene.]

Contact-Reactions in Atopy. I. Contact-Reactions to Silkworm in Atopic Subjects. Albert, M., and Walzer, M.: J. Immunol. **38**: 201, 1940.

Patch tests with an ointment containing 25 per cent defatted powdered silkworm in petrolatum were applied to a series of atopic and nonatopic children and adults. About 50 per cent of the atopic children and 5 per cent of the atopic adults showed positive reactions, whereas there were 4 per cent who reacted among the nonatopic children and none among the nonatopic adults. The reaction, which usually appeared from twenty-four to seventy-two hours after application of the test, appeared at first as a few tiny discrete vesicles. Within twenty-four hours of the beginning of the reaction, there was itching and slight edema of the test area, which was covered with numerous, closely aggregated, discrete vesicles. The reaction then gradually subsided over the course of from one to three weeks.

Control studies demonstrated that this reaction was not caused by the ether extract (oily fraction) of silkworm, nor was it based upon the presence of atopic reagin. In several instances, patients apparently were sensitized by repeated application of the silkworm ointment.

Treatment of Pneumonia With Sulfapyridine: Observations on Toxic Reactions. Detweiler, H. K., Kinsey, H. I., Brown, W. H., and Feasby, W. R.: Arch. Int. Med. **65**: 1144, 1940.

In a group of ninety patients given fairly large doses of sulfapyridine for the treatment of pneumonia, six developed cutaneous rashes, macular to morbilliform in type. In all instances the skin eruption cleared up when the drug was stopped. Approximately an equal number of patients developed the other common toxic symptoms of oliguria, gross hematuria, leucopenia, anemia, or fever.

Some Observations on the Persistence of the Bachman Skin Test and of Eosinophilia After Recovery From Trichinosis. Warren, M., Drake, E. H., and Hawkes, R. S.: Ann. Int. Med. **13**: 2141, 1940.

Of fifty-two persons who were examined during an epidemic of trichinosis in 1935, forty-five were available for re-examination three years later (1938). Twenty

of this group had both eosinophilia and a positive skin test when originally seen. At the time of re-examination, seventeen (85 per cent) still showed a positive skin test. Of eight who originally exhibited a positive skin test and eosinophilia, but no clinical symptoms, 6 still showed a positive skin test (75 per cent). The skin test showed a tendency to become somewhat less marked 3 years after the illness. Eosinophilia was, for the most part, absent at the time of re-examination.

Purpura Hemorrhagica Following Neoarsphenamine and Bismarsen Therapy. Further Studies on Sensitivity to Arsphenamine and Tolerance to Mapharsen. Falconer, E. H., and Epstein, N. N.: Arch. Int. Med. **65**: 1158, 1940.

This paper presents detailed studies of 6 patients, 5 of whom presented purpura hemorrhagica following the administration of an arsenical (in 2 instances, neoarsphenamine, and in 3, bismarsen), and one of whom presented hemorrhagic phenomena without purpuric lesions and without a decrease in platelets. Each of the 5 patients presenting purpura hemorrhagica could tolerate mapharsen without reaction. Test doses of the drugs to which these patients were sensitive resulted in the prompt onset of varying degrees of shock, suggesting to the authors an allergic, rather than a toxic, reaction. A prompt loss of capillary tone is the probable reason for the sudden drop in the platelet count found after the administration of the arsenical. The fairly prompt rise in the platelet count (within twenty-four to forty-eight hours) is taken as evidence that the drop in the count is not caused by the destruction of platelets.

Some Observations on Intracutaneous Reactions in Allergic Eczemas. Haxthausen, H.: Brit. J. Dermat. **52**: 191, 1940.

The author presents evidence which tends to demonstrate that in true allergic eczemas (contact dermatitis) the hypersensitivity is often found in the corium as well as in the epidermis. In patients who are hypersensitive to metals, the intracutaneous injection of 0.1 c.c. of a weak solution of a salt of the offending metal will almost always produce a papular reaction after from twenty-four to forty-eight hours. Such reactions are not found in normal persons. In many instances, within one or more days after the appearance of the papule, pseudopodia-like processes appear about the papule and extend slowly during the next few days as red streaks in the surrounding skin. The author discusses the possible causes of the spread of the reaction along the lymphatics. He believes that a simple spread of the metallic salt is unlikely, since such a spread would be rapid. He suspects that the cause may be a slowly spreading substance produced by the interaction of the antigen and the hypersensitive cells in the skin.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

The Specificity of Oxidized and Reduced Proteins of the Ocular Lens. Ecker, E. E., and Pillemer, L.: J. Exper. Med. **71**: 585, 1940.

Recent studies by the author revealed that species specificity is an individual peculiarity of the keratins and that it is dependent on the oxidation-reduction (redox) state of the sulphydryl grouping in the protein. Since the lens is rich in

sulphydryl sulfur, it was chosen for further studies on the immunologic behavior of this group of proteins.

The lenses of swine, chicken, sheep, and fish (pike) were prepared to avoid denaturation and to maintain the desired redox state of the protein. Rabbits received intravenous injections of 20 mg. of freshly prepared proteins daily for several six-day periods.

Chemical analysis of the various proteins revealed the total nitrogen content of the different proteins to be almost identical. Marked variations were evident in the isoelectric points and in the content of cysteine of the various lens proteins. The proteins secured from swine and sheep lenses were almost identical in their chemical characteristics. The results of cross precipitation reactions indicated that only in distantly separated species, e.g., fish and chicken, is species specificity a prominent characteristic of the lens proteins. In immunologic tests of the proteins from swine and sheep lenses, almost identical results were obtained. A comparison of the chemical analysis of these proteins and their serologic characteristics revealed a marked similarity between chemical composition and immunologic variation.

Oxidized lens proteins precipitated their homologous antisera in lesser degree than the reduced antigen, regardless of whether the homologous antisera were prepared from oxidized or from reduced proteins. These observations suggested that the spatial arrangement and recurrence of sulphydryl-disulfide grouping play a more important part in the specificity of the compounds than the redox state.

Studies on a Purified Antigen from Brucella. Morales-Otero, P., and Gonzáles, L. M.: Am. J. M. Sc. **199**: 810, 1940.

The different methods employed in the preparation of antigens have made correlations of cutaneous hypersensitivity to *Brucella* infection extremely difficult. In the present study, the authors have used a modification of Seibert's technique to prepare a purified-product derivative from *Brucella* cells. This preparation has a fairly constant chemical composition and was used for complement fixation tests and for testing for cutaneous hypersensitivity in both man and animals.

For intracutaneous testing 0.1 ml. of a 0.1 mg. per milliliter solution was used. In man the positive cutaneous reaction was characterized by marked edema and induration at forty-eight hours. In sensitized guinea pigs a violent inflammatory response with neutrophilic infiltration was noted following intracutaneous testing.

In Puerto Rico, where *Brucella abortus* infection is prevalent in cattle, 4.2 per cent of the general population (1,003) using raw milk evidenced positive cutaneous reactions. Of 222 persons in direct contact with cattle, 24.7 per cent gave a positive reaction. At St. Thomas, where no *Brucella* infection exists, no reactions were found among the 441 persons tested. The authors conclude that there is a direct relation between contact with infected material or ingestion of raw milk products and the incidence of cutaneous reactions to *Brucella*.

No correlation was found between the cutaneous reaction to *Brucella* and other immunologic reactions, such as agglutination and complement fixation.

The Histaminase Content of the Tissue of the Rat and the Effect of Histamine Pretreatment. Rose, B., Karady, S., and Browne, J. S. L.: Am. J. Physiol. **129**: 219, 1940.

These studies were undertaken in an effort to determine the source of histaminase in the rat and to note the effect of histamine pretreatment on the histaminase content of living tissue in this animal.

Preliminary experiments indicated that the destruction of histamine in vitro takes place in direct ratio to the amount of histaminase present and that the

destruction of histamine by a fixed amount of histaminase increases in direct ratio to the concentration of histamine present.

Lung, liver, kidney, spleen, small intestine, stomach, and blood were studied in order to determine which tissues were capable of destroying histamine. Of these, only lung and small intestine gave positive results. Four groups of rats, pretreated with subcutaneous injections of histamine for a period of ten days, were killed six hours after the last injection and various tissues were removed for incubation. No increase in the histaminase content of lung tissue was observed following pretreatment with histamine.

According to the authors, it does not seem probable that the rapid inactivation of histamine occurring in the rat following its intravenous injection can be accounted for by histaminase present, in the lung and small intestine of this animal. In support of this is the fact that rat kidney and liver, neither of which contains histaminase, have been shown to be responsible for the greater part of the destruction of intravenously injected histamine. Previous studies have also demonstrated that the rate of disappearance of intravenously injected histamine is not altered in the histamine-pretreated rat.

Thymoxyethyldiethylamine as an Antagonist of Histamine and of Anaphylactic Reactions. Rosenthal, S. R., and Brown, M. L.: J. Immunol. **38**: 259, 1940.

The action of thymoxyethyldiethylamine in the prevention of histamine shock and anaphylactic shock was studied.

A strip of guinea pig ileal muscle, suspended in the Schultz-Dale bath and treated with 0.5 gamma of thymoxyethyldiethylamine for from three to five minutes, did not contract on subsequent exposure to from 0.02 to 0.04 gamma of histamine. Previous studies demonstrated this antagonistic action to be specific since acetylcholine, potassium chloride, barium chloride, and other substances were inhibited only partially or not at all by thymoxyethyldiethylamine. The subcutaneous injection of 40 mg. per kilogram of thymoxyethydiethylamine thirty minutes prior to the intracardiac injection of usually fatal doses of histamine prevented all symptoms of shock except slight malaise. Repetition of these doses of histamine the following day caused death in all of these animals.

The addition of 0.33 mg. of thymoxyethyldiethylamine to the Schultz-Dale bath containing a suspended uterine horn from a passively sensitized guinea pig prevented contraction of the horn following the addition of the specific antigen and also following the addition of histamine.

Sensitized guinea pigs, injected subcutaneously from thirty to forty-five minutes before administration of the shocking dose with 40 mg. per kilogram of thymoxyethyldiethylamine, required a greatly increased dose of antigen to produce fatal anaphylactic shock. Respiratory difficulty, scratching, or convulsions rarely developed in pretreated animals not fatally shocked. They did, however, show signs of malaise and prostration. Animals receiving thymoxyethyldiethylamine twenty-four hours prior to the test dose of antigen were fatally shocked by the minimal lethal dose.

Antibodies to Strychnine. Hooker, S. B., and Boyd, W. C.: J. Immunol. **38**: 479, 1940.

Mono- and di-amino compounds, prepared from mononitrosostrychnine and dinitrosostrychnine were diazotized and coupled with horse serum. The sera of some rabbits, injected thrice weekly for four weeks with each of these compounds, showed weakly positive precipitation reactions when tested with casein-mono-amino and casein-di-amino-strychnine. The antisera to the di-amino compound were markedly inferior in potency. After a month the sera of the same

rabbits, similarly injected with mono-aminostrychnine azohemocyanin (mono-aminostrychnine coupled with the blood proteins of *Limulus polyphemus*) showed antibodies specific for strychnine. These antisera did not precipitate casein. The specificity of the antibody was confirmed by the fact that precipitation with casein-azostrychnine was inhibited by the strychnine alkaloid and some of its amino, nitro, and methoxyl derivatives, but not by morphine or quinine and not even by tryptophane, which, like strychnine, contains the indol nucleus. Quantitative measurement of the specifically precipitable nitrogen in these sera indicated that the quantity of antistrychnine in these sera was small.

A failure to produce antimorphine by a similar technique is recorded.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

The Use of Elimination Diets in Allergy of Childhood. Stoesser, A. V., and Hanson, E.: Journal-Lancet **59**: 452, 1939.

The authors feel that less than 50 per cent of patients who are allergic to certain foods give positive skin tests to those foods. They review the principles involved in the construction of an elimination diet and list examples of diets unlikely to contain allergenic foods. Vitamin and mineral supplements are adequately treated. Common opportunities for error are listed.

Contact Reactions in Atopy. II. Incidence of Contact Reactions with Various Allergens. Albert, M., and Walzer, M.: J. Invest. Dermat. 3: 119, 1940.

The authors describe what may be a new type of skin reaction which is most often elicited in allergic children. A patch test with an ointment containing about 25 per cent of the defatted powdered allergen was applied by the usual adhesive and wax paper technique and was allowed to remain in place for from one to seven days. In case of a positive reaction, small, shiny, discrete vesicles and a little erythema were seen first. They became closely aggregated within twenty-four hours, did not exude, and did not spread beyond the area of contact. The reaction subsided with desquamation usually.

The following allergens were used in testing: silk, feathers, orris root, ragweed, timothy and plantain pollens, cottonseed, cow and goat epitheliums, tobacco, wool, wheat, milk, egg, and corn.

One-half of the atopic children tested gave positive reactions to feathers and silk. Other allergens caused fewer positive reactions. Plantain pollen, egg, wheat, and milk gave no reactions. The positive tests were usually in the 5- to 12-year group and were much less frequent in adults and in nonatopic children.

Sensitivity was apparently induced by the application itself in certain instances with silk, cottonseed, ragweed, and tobacco.

Report on the Home for Asthmatic Schoolchildren in Stockholm. Salen, E. B., Hulting, C., and Nordenfors, B.: Acta med. Scandinav. supp. 89, pp. 85-112, 1938.

Dissatisfied with the progress, or rather absence of progress, being made in the handling of asthmatic children (which was chiefly medicinal in nature), the authors undertook a closer study of skin tests to determine in which direction effort should

be placed. Thirty-six asthmatic children from 8 to 14 years old were tested intracutaneously with extracts of house dust, mites, feathers, molds, human dander, bacteria, horse hair, dog hair, cat hair, cattle hair, and various foods. Twenty-four control children were similarly tested and were entirely negative to house dust and almost all other antigens. To rule out a greater reactivity of the allergic children, 1:10,000 histamine was also used for tests in both groups, and no essential difference in response was found. The reactions to house dust were so much more numerous and marked than the other reactions that effort was directed toward that. Investigation of homes revealed a situation of such crowding that dust control at home seemed out of the question. Therefore, a former schoolhouse was converted into a home for asthmatic children and they were quartered there in as dust-free an environment as possible. Visiting their homes in the afternoon, after attending a near-by school, was permitted the children. The improvement in attendance at school and the freedom from asthma were remarkable in the twenty-two children who were taken into the home. The result was that the home, first started as an independent project, was taken over as a civic project by the city of Stockholm.

Sudden Death in Infantile Eczema. Davies, J. H. T.: Brit. J. Dermat. & Syph. **52**: 182, 1940.

Having seen sudden death occur in hospitalized infants with eczema several years ago, the author was opposed to hospitalization of such cases. He was persuaded, however, on three occasions and for various reasons to deviate from this rule. All three of these consecutive cases terminated fatally with what was thought to be insufficient cause. It is pointed out that such an occurrence is likely to take place in the spring in overnourished infants under 1 year of age. It may be heralded by sudden improvement in the eczema. No satisfactory explanation for such deaths is at hand.

Body Build in Infants. IX. Body Build in Eczema. Bakwin, H., and Bakwin, R. M.: Human Biol. **11**: 269, 1939.

Amplifying a previous study, the authors find again that infants with eczema have, on the average, a wider head, broader face, more widely separated eyes, and larger shoulder, hip, and chest circumferences than are found in a control group. They are slightly taller and considerably heavier as well. Males outnumber females in the eczema group about two to one.

Significance of Inhalant Allergens in the Treatment of Bronchial Asthma of the Child. Stoesser, A. V.: Minnesota Med. **23**: 413, 1940.

In a group of 329 children with asthma, inhalants other than pollens were found to be the chief offenders; pollens were the next most common cause, and foods the least frequent. Among the inhalants, house dust, feathers, and cottonseed were the most common offenders. Hyposensitization in this group was disappointing, but environmental control gave satisfactory results. Sudden changes in the weather precipitated asthma in a considerable number of persons, most of whom were in the house-dust-sensitive group.

The Use of a Soybean Emulsion in a Simplified Regime for the Study and Treatment of Infantile Eczema. Levin, S. J.: J. Pediat. **17**: 79, 1940.

A simplified plan for the study and treatment of infantile eczema is presented. Chief factor in the plan is a commercial soybean emulsion, kreme o'soy, which is

said not to cause diarrhea, excoriated buttocks, vomiting, or refusal, all of which had at one time or another been bothersome when sobee was used.

As corn syrup and dextrimaltose were both found to be antigenic in certain cases, cane sugar replaces them in the soybean formula. Cooked sobee is used as a cereal.

Environmental control and local treatment are along the usual lines, save that a water bath several times a week is found to be helpful. It is of interest that sensitivity to cevitamic acid is reported in two cases. Seventy-seven per cent of the eighty-six cases studied were sensitive to milk clinically, but 35 per cent of these gave negative skin tests to milk. After complete elimination for from six to twelve weeks, heated milk is usually tolerated by the persons who were formerly sensitive to it.

Concerning Exudative Eczematoid With Regard to Food Allergy. Schreus, H. T.: München med. Wchnschr. **86**: 1075, 1939.

While skin tests and complement fixation reactions are of no help in the study of eczema, the leucopenic index promises to be more useful. Having determined an etiological food allergen, desensitization can be undertaken if it is an important foodstuff, either by oral administration of gradually increasing amount or by the use of propeptans. The latter can be freshly and inexpensively prepared at home by the use of pepsin and hydrochloric acid.

When more severe symptoms occur on resumption of ingestion of a food previously eliminated than had occurred with its use prior to elimination, the explanation is probably as follows: With the constant use of the food, there was an almost complete saturation of antibodies so that a sort of anergic state occurred. This balance was broken with the elimination of the food, and a marked rise in antibodies resulted. Usually, common foods eaten daily are concerned with this sort of situation. The patient is much more apt to find out himself which of the more unusual articles of diet bother him.

At times the patient is not only sensitive to a specific protein, but has a parallergic spread of sensitivity to all proteins, especially animal proteins. The sensitivity may be to the less specific split-protein products. The frequent success of a vegetarian diet may rest on this basis.

Eczema of adults also rests chiefly on a food allergy basis. As in infancy, milk is by far the chief offender, with egg and pork following in importance. It may be that eczema at all ages is fundamentally a disease based on milk allergy. Other allergens may act as haptene modifiers of the underlying milk sensitivity. In this way the tolerance of certain allergens only when milk is eliminated would be explained. The patient with eczema is thus an example, not of allergy, but of parallergy or synallergy.

In summary, it is stated that sensitivity to some food constantly ingested is the basis of eczema. Therapy should therefore be directed along the lines of rigid dietary management.

Concerning the Immunity of Newborn Animals. Schneider, L., and Szathmary, J.: Ztschr. f. Immunitätsforsch. **94**: 458, 1938; **95**: 169, 1939. Summary by Manwaring. California & West. Med. **52**: 208, 1940.

Domestic animals can be divided into four groups, depending upon the type of placentation. In cattle, sheep, dogs, and rabbits there is a progressive decrease in the number of tissues separating fetal from maternal circulation. One would therefore expect a progressive increase in transplacental transmission of maternal antibodies. This was shown to be the case, at least for the antibodies of *B. typhosus* and

diphtheria immunization. In calves there was practically no transmission, but in rabbits there was an almost identical antibody titer in newborn and maternal bloods. Human beings resemble the rabbit in the type of placentation, the chorionic epithelium coming into direct contact with the maternal blood.

Colostric feeding raised the antibody titer in all instances, save the rabbit, where a 10 per cent drop occurred as a result of the first colostric feeding. If a similar lack of antibody absorption occurs in the human being, some of the arguments in favor of breast feeding will have to be revised.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Diagnosis and Treatment of Chronic Disease of the Paranasal Sinuses. Williams, H. L., and Mousel, L. H.: Ann. Otol., Rhin. & Laryng. **49**: 466, 1940.

In a general discussion of the subject of the diagnosis and treatment of chronic disease of the paranasal sinuses presented by Williams and Mousel, they state that the fundamental requirement in the treatment of chronic sinusitis is a differential diagnosis accurate enough to prevent the application of formidable surgical procedures to conditions in which they cannot logically be expected to produce any beneficial effect. They further state that it is lack of attention to this important detail that has had the effect of bringing surgical procedures, directed against chronic suppuration in the paranasal sinuses, into disrepute among the uninformed physicians and laymen, not, however, without justification. A great deal of emphasis is placed upon the importance of the diagnosis of allergy and allergy with infection in relation to chronic disease of the paranasal sinuses. The value of cytologic and bacteriologic examination and their correlation with the symptomatology, and x-ray and physical findings are discussed in considerable detail. The indications and technique of various surgical procedures on all the paranasal sinuses are outlined. It is finally concluded that, as far as surgical interference is concerned, an operative technique which logically fits the individual case and which will be adequate to take care of the disease present should be selected.

Nasal Obstruction Caused by Collapse of the Nasal Alae. Lillie, H. I., and Kinsley, S. M.: Ann. Otol., Rhin. & Laryng. **48**: 600, 1939.

Lillie emphasized the importance of considering collapse of the alae of the nose as the cause of nasal obstruction, and he feels that this condition is more frequently present than is generally believed. If a cotton ball tucked into the anterior superior recess of the vestibule gives complete relief of obstruction, the diagnosis is established. Some patients, when the cause of obstruction is pointed out, will be able to correct the condition by correcting the air breathing. In some cases the cotton ball may be used; in others, a silver tube shaped to fit the vestibule. If other methods do not suffice, surgical procedures may be tried. It is important to take this point into consideration in patients with nasal obstruction, particularly in differentiating nasal obstruction due to allergic swelling of the mucosa and mechanical obstruction as described above.

The Upper Respiratory Revenge of the Allergic Child. Tumpeer, I. H.: Illinois M. J., January, 1940.

In discussing the general subject of the upper respiratory revenge of the allergic child, Tumpeer states that in allergy, sinus involvement is an effect rather

than a cause, and sneezing is not characteristic of sinusitis. He also points out that the narrow nasal passage is due to edema of the mucosa rather than to a structural bone defect. The point is also emphasized that tonsillectomy and adenoidectomy per se have no therapeutic benefit in asthma, and that there is no excuse for tonsillectomy on the grounds that fewer colds will result and, therefore, fewer attacks of asthma. Finally, it is emphasized that surgical procedures of all types should be deferred until complete allergic study has been carried out.

Studies of a Vestibular Syndrome Induced in Guinea Pigs by Allergic Reaction. Skoog, Torsten: Acta oto-laryng. 32: supp., 1939.

Skoog reports his experimental observations on the production of a vestibular syndrome produced by making centripetal intracarotid injections of sheep-hemolytic rabbit serum into a larger number of guinea pigs. The investigation was carried out with the idea of locating the site of allergic reaction. The symptoms which followed intracarotid centripetal injection on the right were characterized by certain vestibular phenomena: twisting of the head and the whole body to the left and circus movement to the left, as well as constant ocular deviations and disturbances of the normal caloric and rotatory reactions. The symptoms were regarded as vestibular phenomena of irritation produced by disturbances in the vestibular ganglia of the medulla oblongata, for preliminary removal of the peripheral labyrinths and the cerebellum had no influence on the character of the symptom complex. Histopathologic examination showed an increased capillary permeability in the medullopontile region, with hemorrhages. These changes were verified by intra-vitam staining with acid dyes, with which an intense staining of this region can be observed. Although the results noted were not considered directly applicable to man, they should, no doubt, be of interest regarding the allergic genesis of certain forms of Menière's disease.

Mycotic Infection of the Broncho-Pulmonary Tract. Vadala, A. J.: Ann. Otol., Rhin. & Laryng. 49: 291, 1940.

The subject of mycotic infection of the bronchopulmonary tract is considered in great detail in the presentation by Vadala. He emphasizes the importance of bronchoscopic examination, aspiration, and culture of the bronchial secretions. In these cases differential diagnosis lies between chronic bronchitis, pulmonary tuberculosis, asthma, and bronchiectasis. A number of case reports are presented to emphasize the value of bronchoscopic methods in diagnosis and treatment.

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For relief of the nasal congestion in:
COLDS • SINUSITIS • RHINITIS

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DROPPER

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(AFTER PROETZ)

JELLY

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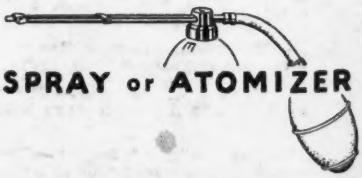

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